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| cLINICAL UTILITY OF MOLECULAR TESTING IN  Myeloid neoplasms with germline *DDX41* mutation  The presence of a pathogenic/likely pathogenic germline mutation in *DDX41* in association with myeloid (or less commonly lymphoid) malignancy defines the WHO category of *Myeloid neoplasms with germline DDX41 mutation*1. This is an autosomal dominant familial syndrome1.  Germline pathogenic/likely pathogenic *DDX41* mutations have been described in approximately 1-3% of MDS and AML2-6.  Germline pathogenic/likely pathogenic *DDX41* mutations in myeloid neoplasms are strongly associated with male gender3-5.  The approximate age of MDS/AML onset in carriers of pathogenic/likely pathogenic *DDX41* mutations is similar to sporadic MDS/AML diagnoses2,4,5 therefore an inherited predisposition to malignancy may not be suspected, particularly in the absence of a strong family history5.  The most frequent somatic mutation that occurs with a germline pathogenic/likely pathogenic *DDX41* mutation is a second *DDX41* mutation (70-80% of cases with a myeloid neoplasm)2,5. The Arg525His is the most commonly observed somatic *DDX41* mutation, usually seen at low variant allele frequency (<30%)2,3,5.  Somatic *DDX41* mutations are infrequntly observed in MDS/AML in the absence of an identified germline *DDX41* mutation5,7.  Many additional somatic mutations commonly found in sporadic myeloid neoplasms have also been observed in myeloid neoplasms with germline pathogenic/likely pathogenic *DDX41* mutations including, but not limited to *ASXL1*, *DNMT3A*, *TET2*, *EZH2*, *CUX1*, *TP53*, *JAK2* and *SRSF2*3,5,7.  The majority of myeloid neoplasms with germline pathogenic/likely pathogenic *DDX41* mutations have a normal karyotype2-5.  The detection of a suspected germline *DDX41* mutation should prompt referral to a genetic service for evaluation of germline status and screening of appropriate family members. This is particularly important in the context of screening potential related donors for allogeneic stem cell transplant.  References  **1.** Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. **2.** Bannon SA, et al. Next-Generation Sequencing of DDX41 in Myeloid Neoplasms Leads to Increased Detection of Germline Alterations. *Front Oncol* 2021; **10**: 582213. **3.** Quesada AE, et al. DDX41 mutations in myeloid neoplasms are associated with male gender, TP53 mutations and high-risk disease. *Am J Hematol* 2019; **94**(7): 757-66. **4.** Polprasert C, et al. Inherited and Somatic Defects in DDX41 in Myeloid Neoplasms. *Cancer Cell* 2015; **27**(5): 658-70. **5.** Sebert M, et al. Germline DDX41 mutations define a significant entity within adult MDS/AML patients. *Blood* 2019. **6.** Lewinsohn M, et al. Novel germ line DDX41 mutations define families with a lower age of MDS/AML onset and lymphoid malignancies. *Blood* 2016; **127**(8): 1017-23. **7.** Makishima H, et al. Clinical Impacts of Germline DDX41 Mutations on Myeloid Neoplasms. *Blood* 2020; **136**(Supplement 1): 38-40. |