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| cLINICAL UTILITY OF SOMATIC MUTATION TESTING IN PATIENTS WITH A GERMLINE PREDISPOSITION TO MYELOID NEOPLASMS  Germline predisposition syndromes are heterogeneous with regards to their causative genetic mutations, clinical manifestations and risk of progression to overt MDS and/or AML1.  Progression to MDS or AML may be associated with the acquisition of somatic mutations and/or chromosomal abnormalities. However high quality prospective data to guide surveillance testing in patients with an inherited germline predisposition to myeloid malignancy are currently lacking.  The detection of acquired (somatic) mutations in a patient with a germline predisposion to myeloid neoplasm must be interpreted alongside other clinicopathologic features.  While the spectrum of somatic mutations and chromosomal aberrations acquired in the setting of germline predisposition syndromes may overlap with those seen in sporadic myeloid neoplasms, there are also some marked distinctions (see below).  *GATA2* germline disease is enriched for somatic mutations in *ASXL1* and *STAG2*, which may be observed both prior to and at MDS onset2,3. Mutations in *DNMT3A*, *BCOR* and *SETBP1* are also recurrent whereas *TET2* and splicing factor gene mutations appear to be rare2,3. Somatic *GATA2* mutations are rarely observed4. GATA2-related MDS is associated with monosomy 7, der(1;7) and trisomy 83,5.  *SAMD9* and *SAMD9L*-related MDS are assocated with chromosome 7 aberrations which may result in the loss of the mutant allele6. In patients with a germline *SAMD9* or *SAMD9L* mutation, secondary somatic loss-of-function mutations in *SAMD9* and *SAMD9L* (nonsense and frameshift) *in cis* with the germline gain-of-function mutation have also been observed6,7.  Clonal haematopoiesis (CH) due to acquired gain-of-function mutations in *CSF3R* is frequently observed in severe congenital neutropenia (SCN)8. *CSF3R* and *RUNX1* mutations are frequently found in SCN patients who develop AML and these often co-occur9. Additional somatic mutations described in SCN patients who develop AML or MDS include *EP300, FLT3* and *CBL9*. Monosomy 7 is also described in cases of leukaemic transformation9.  Shwachman-Diamond syndrome (SDS) is significantly enriched for somatic mutations in *TP53* whereas typical CH mutations such as *DNMT3A*, *TET2* and *ASXL1*, are rare10,11. Progression of *TP53*-mutated clones towards leukaemia is driven by development of biallelic alterations of the *TP53* locus via deletion, CN-LOH, or point mutation8,11.  Progression to AML in patients with a germline *CEBPA* mutation is typically associated with an acquired *CEBPA* mutation in the remaining wildtype *CEBPA* allele12,13. Disease recurrence after chemotherapy may be associated with a different spectrum of mutations, including acquisition of a new somatic *CEBPA* mutation not present at diagnosis13.  CH is highly prevalent in asymptomatic *RUNX1* carriers14-16. Progression to haematological malignancy in patients with a germline *RUNX1* mutation has been associated with acquistion of a somatic *RUNX1* mutation in some patients17,18. Other mutations also seen in sporadic myeloid neoplasms (e.g *TET2, EZH2, SRSF2, SF3B1, NRAS)* have been observed both prior to and at diagnosis of a myeloid neoplasm14,15.  The most frequent somatic mutation that occurs with a germline pathogenic/likely pathogenic *DDX41* mutation is a second *DDX41* mutation (~80% of cases with a myeloid neoplasm)19,20. The Arg525His is the most commonly observed somatic *DDX41* mutation, usually seen at low variant allele frequency (<30%)19-21.  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*, *TP53*, *JAK2* and *SRSF2*20-22. The prognostic significance of these comutations is currently uncertain.  Leukemogenesis has a unique molecular pattern in germline *MBD4*-variant carriers characterised by C > T transitions, bi-allelic *DNMT3A* mutations, and mutations in either *IDH1* or *IDH2*23.  REFERENCES  **1.** Alter BP, et al. 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