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| cLINICAL UTILITY OF MOLECULAR TESTING IN  MYELOID PROLIFERATIONS ASSOCIATED WITH DOWN SYNDROME  DIAGNOSTIC utility  Transient abnormal myelopoiesis (TAM) occurs in ~10% of newborns with Down Syndrome (DS)1.  Trisomy 21 mosaicism should be considered in an infant who develops features of TAM but lacks features of DS2.  In approximately 20% of cases, TAM evolves into acute myeloid leukaemia (AML), typically with megakaryoblastic features2,3.  AML associated with DS may be preceded by TAM, or by a prolonged myelodysplastic syndrome (MDS)-like phase. MDS and overt AML in DS have no significant biological differences, and thus the term “myeloid leukaemia associated with DS (ML-DS)” encompasses both MDS and AML for these patients4.  One or more somatic (acquired) *GATA1* variants is detectable in the majority of TAM and ML-DS5-7. The *GATA1* mutant allele burden has shown to correlate with the peripheral blood blast percentage1.  Approximately 5-20% of newborns with DS have detectable *GATA1* variants without features of TAM (“silent TAM”)1,8.  The value of monitoring mutant *GATA1* clones after diagnosis of TAM is currently not clear9.  ML-DS arises from a *GATA1*-mutant clone that has acquired additional mutations in cohesion complex genes (e.g. *RAD21*,*STAG2*), *CTCF*, epigenetic regulators (e.g. *EZH2*), *TP53* and activated signalling pathway genes (e.g. *NRAS, KRAS*)10.  Children aged >5 years with DS and AML may not have *GATA1* variants and such cases are considered to be conventional AML rather than DS-AML4.  REFERENCES  **1.** Roberts I, et al. GATA1-mutant clones are frequent and often unsuspected in babies with Down syndrome: identification of a population at risk of leukemia. *Blood* 2013; **122**(24): 3908-17. **2.** Gamis AS, et al. Natural history of transient myeloproliferative disorder clinically diagnosed in Down syndrome neonates: a report from the Children's Oncology Group Study A2971. *Blood* 2011; **118**(26): 6752-9; quiz 996. **3.** Klusmann JH, et al. Treatment and prognostic impact of transient leukemia in neonates with Down syndrome. *Blood* 2008; **111**(6): 2991-8. **4.** Swerdlow S, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. **5.** Greene ME, et al. Mutations in GATA1 in both transient myeloproliferative disorder and acute megakaryoblastic leukemia of Down syndrome. *Blood Cells Mol Dis* 2003; **31**(3): 351-6. **6.** Hitzler JK, et al. GATA1 mutations in transient leukemia and acute megakaryoblastic leukemia of Down syndrome. *Blood* 2003; **101**(11): 4301-4. **7.** Wechsler J, et al. Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down syndrome. *Nat Genet* 2002; **32**(1): 148-52. **8.** Goemans BF, et al. Sensitive GATA1 mutation screening reliably identifies neonates with Down syndrome at risk for myeloid leukemia. *Leukemia* 2021; **35**(8): 2403-6. **9.** Bhatnagar N, et al. Transient Abnormal Myelopoiesis and AML in Down Syndrome: an Update. *Current Hematologic Malignancy Reports* 2016; **11**(5): 333-41. **10.** Yoshida K, et al. The landscape of somatic mutations in Down syndrome-related myeloid disorders. *Nat Genet* 2013; **45**(11): 1293-9. |