Molecular pathology selected abstracts

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Insights into *DDX41* MDS/AML predisposing gene variants

January 2024—*DDX41* is involved in multiple cellular processes, including RNA metabolism and splicing. Inherited variants have been linked to an increased risk of the blood neoplasms myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Unlike people with other hereditary hematologic malignancy-associated genes, people with *DDX41* germline pathogenic variants are predisposed to develop late-onset myeloid neoplasms. Recent reports suggest that people who have AML with *DDX41* mutation have longer overall survival and a higher treatment response rate than those with *DDX41* wild-type AML and favorable-risk AML. Small retrospective studies also suggested that *DDX41*-mutated AML is more sensitive to treatment with Venetoclax plus hypomethylating agents than is sporadic AML. A recent article in *Blood* (Kovilakam SC, et al. 2023;142:1185–1192) detailed a comprehensive population-level analysis of 454,792 adult participants in the UK Biobank. The analysis assessed the epidemiologic characteristics, clinical features, and malignancy risk associated with germline pathogenic variants in *DDX41*. The authors found that approximately one in 129 people from their data set carried a nonsynonymous germline variant in *DDX41* and approximately one in 429 had a pathogenic variant. Of the 3,538 *DDX41* pathogenic variant carriers, 25 developed MDS and 20 developed AML after initial sample collection. The median age at MDS/AML onset was 71 years. The variants among the 45 people who developed MDS/AML were truncating (n=21), start-lost (n=7), missense (n=16), and splice site (n=1). Using logistic regression with age, gender, smoking status, and genetic ethnicity as covariates, the authors found that the odds ratios for developing MDS/AML were 15.12, 12.89, and 7.49, respectively, for truncating, start-lost, and pathogenic missense variants. The rare variant R53Afs*16 was found to impart a very high risk, with four of 16 carriers developing MDS/AML, compared with more common pathogenic variants, such as D140Gfs*2 and start-lost. The authors also investigated possible links between *DDX41* variants and myeloproliferative neoplasms, lymphomas, and other cancers but did not find significant associations. Looking for other hallmarks of myeloid disease development, the authors investigated blood count results for the 32 people with available data who developed AML or MDS after initial sampling. They found that mean red cell volume was higher in these people than in *DDX41* pathogenic variant carriers who did not develop MDS/AML. Their data also showed that *DDX41*-mutated MDS/AML did not generally develop through progression from clonal hematopoiesis. Links between DEAD-box RNA helicases and genomic stability have been reported, but the authors did not find significant differences in somatic mutation rates between *DDX41*-mutant AML patients and sporadic AML patients. Overall, the authors provided a comprehensive description of *DDX41* mutations from their large data set. While *DDX41* pathogenic variants were relatively common in this study population, the absolute risk of *DDX41* pathogenic carriers developing MDS/AML was 3.21 percent (5.50 percent in males and 1.37 percent in females), which is lower than estimates derived from prior studies of the relatives of *DDX41*-mutated MDS/AML patients.

Kovilakam SC, Gu M, Dunn WG, et al. Prevalence and significance of *DDX41* gene variants in the general population. *Blood*. 2023;142(14):1185–1192.

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Nanaa A, He R, Foran JM, et al. Venetoclax plus hypomethylating agents in *DDX41*-mutated acute myeloid leukaemia and myelodysplastic syndrome: Mayo Clinic series on 12 patients. *Br J Haematol*. 2023. doi:10.1111/bjh.19105

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Relevance of testing for APOL1 in focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis describes a pattern of kidney injury that causes nephrotic syndrome in approximately 40 percent of adult and 20 percent of pediatric patients. Renal podocytes are specialized cells that maintain the kidney's ability to filter blood. Podocyte damage and dysfunction due to a variety of mechanisms causes nephrotic syndrome (inappropriate loss of blood proteins in urine), which can lead to significant morbidity. Earlier studies identified the gene apolipoprotein L1 (*APOL1*), which is associated with an increased risk for focal segmental glomerulosclerosis (FSGS) and other types of kidney disease in people of African ancestry versus European ancestry. Subsequent studies found a set of risk variants (G1 and G2) that confer up to 10-fold greater odds of FSGS-attributed kidney failure. It is estimated that more than 3 million people of African ancestry in the United States carry two risk variants. APOL1 protein is secreted into the blood to form a lytic factor that protects against the parasitic protozoa trypanosomes. Subspecies of trypanosomes present in sub-Saharan Africa developed mechanisms that inactivate APOL1. This led to *APOL1* G1 and G2 variants, which inactivated the resistance-associated factors. This adaptation took place after people began migrating from Africa to other continents, which is why these variants occur mainly in African people (primarily West Africans) and in those of recent African descent. Renal podocytes appear to be vulnerable to the damaging effects of G1 and G2 variants, possibly via similar means by which trypanosomes are killed. Yet *APOL1* testing has not been widely adopted in the clinical setting, as some believe there is a lack of definitive evidence about the causal link between *APOL1* risk variants and health outcomes. The ongoing National Institutes of Health-funded APOLLO study is prospectively assessing the effects of *APOL1* renal-risk variants on the outcomes of kidney donors and kidney transplant recipients of recent African ancestry. *The New England Journal of Medicine* (Egbuna O, et al. 2023;388:969–979) reported data on a single-group, open-label, phase 2a clinical study of inaxaplin, a selective oral, small-molecule inhibitor of APOL1, in participants with two *APOL1* pathogenic variants and biopsy-proven FSGS. The primary efficacy outcome was the percent change from the baseline urinary protein-to-creatinine ratio at week 13. The study showed a rapid and approximately linear mean change in the urinary protein-to-creatinine ratio of −47.6 percent at week 13. In an analysis that included all 16 study participants, regardless of whether they adhered to inaxaplin treatment, the mean change in the urinary protein-to-creatinine ratio at week 13 was −44 percent. One participant did not have a reduction. Preclinical in vitro and in vivo mouse studies were also reported and showed that inaxaplin bound directly to the APOL1 protein, inhibited APOL1 channel function, and reduced proteinuria in a transgenic mouse model of *APOL1*-mediated kidney disease. The authors noted the limitations of their small-cohort, short-duration, nonplacebo-controlled study but reported that an ongoing phase 2–3 placebo-controlled trial is addressing these concerns. If the trial proves successful and the findings of the APOLLO study affirm the clinical relevance of APOL1, demand for APOL1 clinical testing will likely increase.

Egbuna O, Zimmerman B, Manos G, et al. Inaxaplin for proteinuric kidney disease in persons with two *APOL1* variants. *N Engl J Med*. 2023;388(11):969–979.

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Smith JD, Agrawal A, Wicklund C, et al. Implementation of a culturally competent *APOL1* genetic testing programme into living donor evaluation: A two-site, non-randomised, pre-post trial design. *BMJ*. 2023;13. doi:10.1136/bmjopen-2022-067657

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Williams WW, Ingelfinger JR. Inhibiting APOL1 to treat kidney disease. *N Engl J Med*. 2023;388(11):1045–1049.

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