

Germline mutations associated with acute myeloid leukemia.

Aneta Bąk¹, Katarzyna Skonieczka¹, Anna Jaśkowiec², Anna Junkiert-Czarnecka¹, Marta Heise¹, Maria Pilarska-Deltow¹, Stanisław Potoczek², Maria Czyżewska³, Olga Haus¹.

¹Department of Clinical Genetics, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland.

²Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Medical University in Wrocław, Poland.

³Department of Hematology, Municipal Hospital in Toruń, Poland.

Keywords: germinal mutations, acute myeloid leukemia, AML, *SAMD9*, *SAMD9L*, *KMT2A*, *RUNX1*, *CEBPA*, *DDX41*, *TERT*, *GATA2*, *IDH2*, *ETV6*.

Introduction: Recently, an important progress in the research on molecular pathogenesis of acute myeloid leukemia (AML) as well as in the identification of new diagnostic markers and prognostic factors has been noted. The research carried out so far has allowed the identification of some hereditary mutations predisposing to AML. However, in most families with the history of this disease, the hereditary genetic basis has not been found. Only small proportion of patients (4-10%) with AML have germline mutations identified.

The main aim of the study was to detect germline pathogenic variants in genes: *SAMD9*, *SAMD9L*, *KMT2A*, *RUNX1*, *CEBPA*, *DDX41*, *TERT*, *GATA2*, *IDH2*, and *ETV6*. Particular aims were: to assess the frequency of the variants in the group of patients with AML and the control group, and to evaluate the relationship between their presence and the risk of AML development.

Material and methods: The molecular analysis was carried out in 103 patients (54 men and 49 women) with AML. The median age at AML onset was 56 years (18-79). 39.8% (41/103) of patients reported at last one first- or second-degree relatives with cancer. The control group consisted of 103 people with no cancer diagnosis at the time of specimen collection and no family history of cancer. Analysis was performed with NGS and Sanger sequencing. The mutations were searched for in DNA from peripheral blood. In variant-positive patients, the constitutional character of a variant was verified by analysis of DNA from buccal swabs.

Results: In the investigated group, 12 germline pathogenic(P)/likely pathogenic(LP) variants were identified in *SAMD9*, *RUNX1*, *CEBPA*, *ETV6* and *IDH2* genes in 11 patients with AML. Two different germline pathogenic variants, in *ETV6* (c.1075C>T) and *CEBPA* (c.590_591insACCCGC) genes, were detected in one patient. In *CEBPA* gene, five germline pathogenic variants were detected: c.590_591insACCCGC in four patients (incl. the patient mentioned above), and c.337_344del in one patient. In *RUNX1* gene three germline pathogenic variants were found: c.506_507dupG, c.602G>A, c.596G>A - in a single patient each. In the *IDH2* gene c.419G>A likely pathogenic variant occurred in two patients, and in *SAMD9* LP variant c.3730_3731insTTGCG in one patient. Additionally, two germline variants of undetermined clinical significance (VUS) were detected – one in *KMT2A* gene (c.7114C>T) and one in *DDX41* gene (c.1302+67_1303-67insAG) - each in a single patient. In the control group, we detected one pathogenic germline variant (c.590_591insACCCGC), in the *CEBPA* gene. It was detected in a 27-year old healthy woman with no family history of cancer.

Comment: Patients with acute myeloid leukemia demonstrated a higher frequency of pathogenic/likely pathogenic germline variants in *SAMD9*, *RUNX1*, *CEBPA*, *ETV6*, and *IDH2* genes compared to the control group, which confirms the role of these variants in the development of AML. The median age at the onset of AML in patients with P/LP germline variants was significantly lower than in patients without them. The results of our research suggest a need to enlarge the study group as well as to carry out the family studies. Finding of AML susceptibility genes can help to fully understand its pathogenesis and to identify persons at high risk of the disease. The search for germline gene variants in AML is also a very promising approach to develop new treatment options.