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Prognostic Impacts and Dynamic Changes of Cohesin Complex Gene Mutations in *de novo* Acute Myeloid Leukemia

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Mutations in the cohesin complex genes have been reported in myeloid malignancies, but their prognostic implication and dynamic changes during the clinical course in acute myeloid leukemia (AML) remain to be defined. We studied 391 adult patients with newly diagnosed *de novo* non-M3 AML and found 37 (9.5%) had cohesin gene mutations, most prevalent in *RAD21* (3.8%) and *STAG2* (3.1%). Cohesin mutations were inversely associated with complex karyotype and unfavorable-risk cytogenetics. The presence of cohesin gene mutations predicted better clinical outcomes and was an independent favorable factor for both overall survival and disease-free survival, irrespective of other prognostic factors. A scoring system incorporating cohesin mutations and other prognostic factors could well stratify the patients into different risk groups, which could be validated in another independent cohort. Serial analyses in 116 patients by next generation sequencing showed that two patients lost the original cohesin mutations during disease evolution, while none of the patients without the mutation acquired a novel one at relapse. Ingenuity Pathway Analysis revealed *ERK1/2* as a hub gene in cohesin mutation-associated biological pathways. Furthermore, Gene Set Enrichment Analysis demonstrated that cohesin gene mutations were closely associated with several biological pathways involved in hematopoiesis/myeloid/blood cell-related functions. In conclusion, cohesin gene mutations predict favorable prognosis in AML patients. They may not be critical in disease progression since none of the cohesin-wild patients acquired the mutation during follow-ups.