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Recurrent clinically significant mutations in acute myeloid leukemia: analysis of the cancer genomics database and proprietary data on the CBioportal

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INTRODUCTION & AIM

According to the literature, the frequency of mutations in genes associated with the development of acute myeloid leukemia (AML) varies significantly.

The objective of this study was to obtain up-to-date data on the prevalence of mutations in the "hot spots" of the *FLT3, NPM1, IDH1, IDH2,* and *DNMT3A* genes in AML.

METHOD

An analysis of NGS data from 1567 patients with AML presented in the cancer genomics database on CBioportal [1] and 124 Russian patients with AML was performed.

RESULTS & DISCUSSION

According to the database analysis, at the time of the diagnosis of the disease, 46.6% of patients had mutations in *DNMT3A* p.R882, *NPM1* p.W288Cfs*12, *FLT3*-ITD, *FLT3*-TKD, *IDH1* p.R132, and *IDH2* p.R140.

Only in a third of cases (30.1%) did the *DNMT3A* mutation of R.R882 occur in patients in an isolated variant.

In 47.4% of cases, it was combined with *NPM1* p.W288Cfs*12, in 34.1% with mutations in the hot spots of the *FLT3* gene, and in 23.0% with recurrent mutations in *IDH1* and *IDH2*. At the same time, the combination remains highly significant ($p<0.001$) even after adjusting for the multiplicity of comparisons ($q<0.001$).

As can be seen from the Table, mutations *IDH1* R.R132 and *IDH2* R.R140 are mutually exclusive events in AML.

Table. Assessment of the combination of mutations in the "hot spots" of genes in AML according to the CBioportal

Mutation1	Mutation2	Log2 Odds Ratio	p-value	q-value	Tendency
DNMT3A p.R882	*NPM1* p.W288Cfs*12	2,421	<0,001	<0,001	Co-occurrence
DNMT3A p.R882	*FLT3-ITD* FLT3-TKD	1,055	<0,001	<0,001	Co-occurrence
DNMT3A p.R882	*IDH1* p.R132	1,412	<0,001	<0,001	Co -occurrence
FLT3-ITD *FLT3*-TKD	*NPM1* p.W288Cfs*12	1,896	<0,001	<0,001	Co -occurrence
IDH1 p.R132	*IDH2* p.R140	-2,216	0,002	0,005	Mutual exclusivity

In Russian AML patients, the mutation rates in the "hot spots" of genes generally corresponded to the data from the C-Bioportal cancer genomics database and amounted to the following: *DNMT3A* p.R882 - 7.3%; *NPM1* p.W288Cfs*12 - 15.3%; *FLT3*-ITD - 14.5%; *FLT3*-TKD1 - 4.0%; *IDH1* p.R132 - 5.6%; *IDH2* p.R140 - 10.5% (see Figure).

CONCLUSION

The data obtained indicate that in 40-50% of AML cases, clinically significant recurrent mutations in one or more of the studied genes are detected at the onset of the disease. Mutations for which targeted drugs (FLT3, IDH1, and IDH2 inhibitors) have been developed occur in 35% of patients. In one-fifth of cases (18.1%) of AML, *NPM1* p.W288Cfs*12 is detected, which can be used as an independent target for the molecular assessment of minimal residual disease.

REFERENCE

1. Gao J. et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal. 2013; 6(269): pl1. doi: 10.1126/scisignal.2004088.

Figure. The spectrum of mutations in the analyzed "hot spots" of the *FLT3, NPM1, IDH1, IDH2, DNMT3A* genes in Russian AML cases