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ELEVENTH ANNUAL MEETING

MUTATIONS WITH UNKNOWN CLINICAL SIGNIFICANCE - ANOTHER WAY TO DEVELOP RESISTANCE IN PATIENTS WITH CML?

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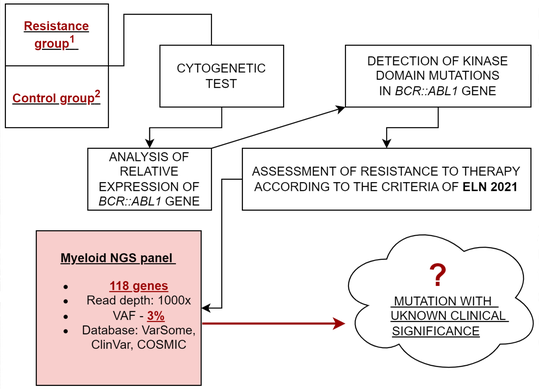
INTRODUCTION

Tyrosine kinase inhibitors (TKIs) have been successfully used to treat patients with chronic myeloid leukemia (CML). Despite the existence of several generations of inhibitors, some patients may develop resistance to TKIs. One of the causes of resistance is the presence of a mutation in the kinase domain of the *BCR::ABL* chimeric gene; however, *BCR::ABL*-independent mechanisms of resistance development are still unknown.

AIM

- Using NGS data to evaluate the impact of mutations with unknown clinical significance on the development of resistance to TKIs

METHOD

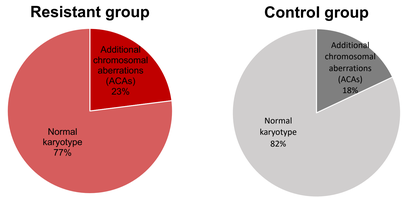


1 - 32 patients with resistant CML (18 men and 14 women) with a median age of 44 (IQR 14-74 years);

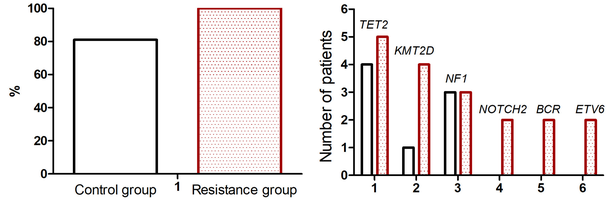
2 - 11 patients who responded to TKI therapy (5 men and 6 women) with a median age of 58 (IQR 33-75 years).

RESULTS

- Cytogenetic analyses



- Number of patients with mutations of unknown clinical significance

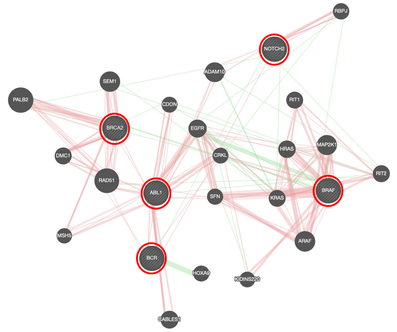


- In 47 % of patients, pathogenic mutations and ACAs were not found. In some of these patients, a major molecular response was not achieved after several years of therapy, and two patients progressed to the blast phase after 9 and 18 months from the start of therapy.

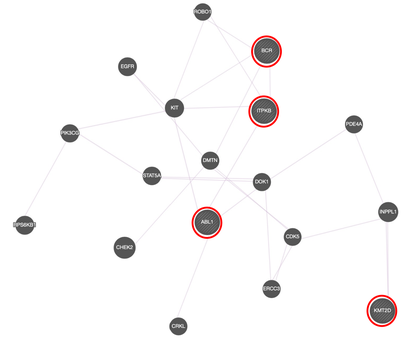
Control group
Resistance group

- Combinations of mutations with unknown clinical significance have been found in blast patients: *BRAF, NOTCH2, BRCA2* and *KMT2D, ITPKB.*

- Interactome *BRAF, NOTCH2, BRCA2*



- Interactome *KMT2D, ITPKB*



- Red lines - protein-protein interactions
- Green lines - gene-gene interactions
- Purple lines - co-expression

CONCLUSIONS

The next generation sequencing makes it possible to identify not only pathogenic mutations, but also mutations with unclear clinical significance. Genes with mutations of unclear clinical significance are involved in many biological processes, namely, they are links in signaling pathways. So the search for their interactions at different levels of the organization can find one of the reasons for the development of resistance to therapy.

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