DEVELOPING ARTIFICIAL INTELLIGENCE-BASED TRANSCRIPTOMIC SIGNATURE FOR SELECTING PATIENTS WITH HOXA-MEIS1 PATHWAY ABNORMALITIES FOR THE TREATMENT WITH MENIN INHIBITORS

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INTRODUCTION

The menin-KMT2A complex plays a major role in activating the HOXA-MEIS1 pathway. Abnormalities in this pathway lead to leukemogenesis. KMT2A gene rearrangement (KMT2Ar) and the expression of various KMT2A fusion genes is a common driving abnormality in pediatric acute myeloid leukemia (AML) and in subgroup of adult AML. In such leukemia, disrupting the menin-KMT2A complex using menin inhibitors has been established as an effective therapy in AML. However, multiple mechanisms other than KMT2Ar can activate the HOXA-MEIS1 pathway and these cases may respond to menin inhibitors.

AIM

We hypothesized that KMT2Ar leads to generalized RNA signature in leukemic cells and this signature can be generated by mechanisms other than KMT2Ar. Using transcriptomic data from AML cases with KMT2Ar, we established a unique expression signature for KMT2Ar AML using artificial intelligence (AI) model. Then we used this AI model for testing KMT2A-negative (KMT2An) AML cases for the presence or absence of such signature.

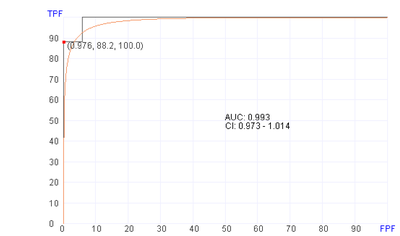
METHOD

RNA was extracted from the bone marrow samples of 759 cases with AML. The RNA was sequenced by next generation sequencing (NGS) using a targeted RNA panel of 1600 genes. RNA was quantified using transcript per million (TPM). Of the 759 AML cases 52 were KMT2Ar positive and 707 were KMT2An. A set of 102 KMT2An cases and the 52 KMT2Ar (total 154) was used to establish the KMT2Ar signature and the rest of the KMT2Arn cases (N=657) were used for testing. Bayesian statistics were used to rank the genes that distinguish between KMT2Ar and KMT2An, then eXtreme Gradient Boosting (XGBoost) was used to establish the KMT2Ar signature. Two thirds of the 154 cases were used for training and one third was used for testing the model. A score for the combination of relevant genes with a cut-off point was established that distinguish TMT2Ar from KMT2An. The same Bayesian/XGBoost algorithm was used to test the rest of the KMT2An AML cases.

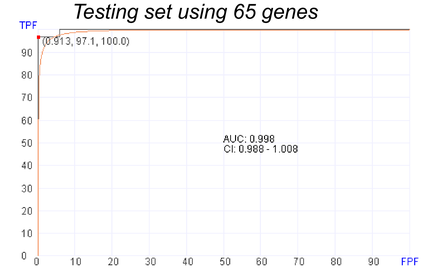
RESULTS

Gene signature distinguishes KMT2Ar from KMT2An

Testing set using 5 genes: TRAF2, TRAF5, TRAF3, CCND2, NEDD4



Testing set using 65 genes

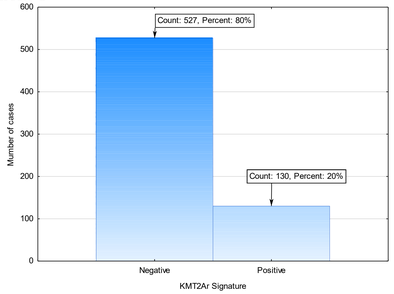


Significant difference in gene expression between KMT2Ar and KMT2An groups

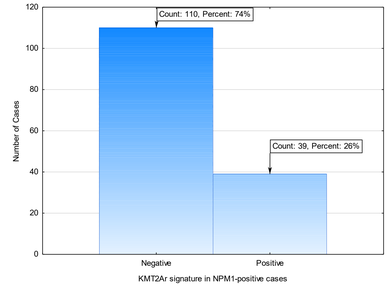
118 genes showed LogFDR <3 . Top ones are listed below

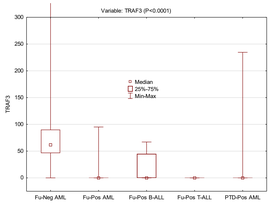
Gene	KMT2A Rearrangement - positive	KMT2A Rearrangement - Nrgstive	LogFDR
TRAF2	1.0167	4.4411	-Infinity
TRAF3	0.3734	4.1565	-Infinity
TRAF5	0.3042	4.4758	-Infinity
NEDD4	3.1021	4.6197	-10.2666152
MACROD1	2.9598	4.0768	-10.2534537
PSIP1	6.232	7.0139	-9.63454739
AKR1C3	3.6271	5.1451	-8.56553892
PRDM16	0.5704	2.1617	-8.47699105
SMARCA5	5.7633	6.3703	-7.8614396
RABEP1	5.3646	6.0993	-7.75475646
ATRX	5.4994	6.1655	-7.65427804
PHF6	4.5841	5.277	-7.5323275
ERC1	4.3872	5.0927	-7.11730317
EZH2	5.4248	6.2185	-7.0873896
HSP90AA1	7.9844	8.6723	-6.96607518
GNA11	1.9724	3.0777	-6.78939369
ANGPT1	2.8882	4.8634	-6.78732163
GRB10	3.1485	4.6395	-6.76692595
RPS6KA2	2.026	3.0818	-6.54653807
FUT1	0.8944	2.2216	-6.49853446
CDK8	3.9493	4.6136	-6.46933887
HGF	3.4077	5.0678	-6.45602409
COMMD1	4.7839	5.3043	-6.4497767
STRN	4.2571	4.7406	-6.38511005
DDX10	4.5153	5.2684	-6.18026759

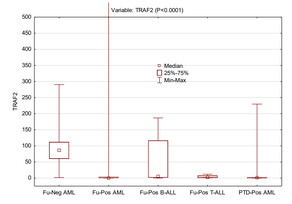
20% of 657 AML cases were positive for KMT2Ar signature

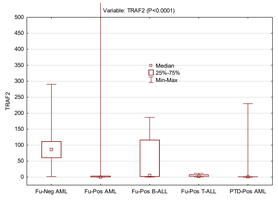


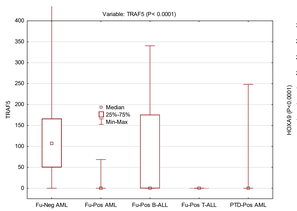
26% of 149 NPM1 mutation-positive cases were also positive for KMT2Ar signature

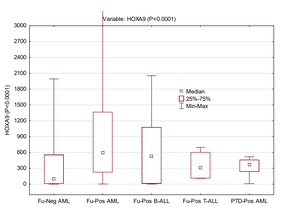












CONCLUSIONS

- KMT2A rearrangement leads to a unique transcriptomic signature activating HOXA-MEIS1 pathway.
- This signature can be used to identify acute leukemia that lack rearrangement but with activated HOXA-MEIS1 pathway
- AI can identify these cases for treatment with menin inhibitors.
- Only 5 genes in the signature can be reliable for predicting KMT2Ar-like cases but 65 genes will provide almost 99.8% accuracy in predicting these cases
- 2 of these genes (CCND2 and NEDD4) are downstream of the HOX9A-MEIS1 and 3 (TRAF2, TRAF3 and TRAF5) are indirectly relevant by activating NF-kB.
- Using this signature, 20% of AML that do not carry KMT2A rearrangement are KMT2Ar-like
- Clinical trial treating KMT2A-like cases with menin inhibitor are justified.

CONTACT INFORMATION

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