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ORAL ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

UBTF Tandem Duplications in Pediatric MDS and AML: Implications for Clinical Screening and Diagnosis

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Recent genomic studies in adult and pediatric acute myeloid leukemia (AML) demonstrated recurrent in-frame tandem duplications (TD) in exon 13 of upstream binding transcription factor (*UBTF*) (PMID: 35176137, PMID:37085611). *UBTF*-TDs are subtype-defining genomic alterations associated with poor outcomes that account for ˜4.3% of AMLs in childhood and up to 3% in adult AMLs under the age of 60. *UBTF*-TD AMLs are characterized by *HOXA/HOXB* dysregulation, trisomy 8 or normal cytogenetics and frequent *FLT3*-ITD and/or *WT1* mutations. A more comprehensive investigation into the clinicopathological features of *UBTF*-TD AMLs is needed to better understand disease features for appropriate diagnosis and to develop more effective therapies.

Here, we present 94 unique pediatric cases harboring a tandem duplication in exon 13 of *UBTF* with a median size of 60bp (range 21-1173bp). Of these 94 cases, 6 (6.4%) were diagnosed with childhood MDS with increased blasts (WHO), suggesting that like in adults, *UBTF*-TDs are not only confined to AML. *UBTF*-TD AMLs are associated with an overall lower median white blood cell (WBC) when compared to other common *HOXA/B* dysregulated leukemias (*UBTF*-TD median = 10.2x10^{9}/L, *NPM1*-mutation median = 21.8x10^{9}/L, *NUP98*-rearranged (*NUP98r*) median = 97x10^{9}/L). Available immunophenotyping on 32 U*BTF*-TD tumors demonstrated positivity for HLA-DR (31/31; 100%), CD117 (28/29; 95%), and CD34 (26/30; 86%) with variable positivity for CD7 (17/30; 56%) and CD64 (13/25; 52%). A limited number of cases tested for CD123 (n=11) and CD11c (n=15) were all positive for the respective marker. Furthermore, morphologic assessment of these cases revealed pleomorphic blasts with occasional Auer rods and increased immature myeloid cells with salmon-colored granules, commonly with background multilineage dysplasia and increased erythroid precursors.

At the transcriptional level, *UBTF*-TD leukemias are largely similar to *NPM1*-mutated and *NUP98::NSD1* AMLs with the exception of *UBTF*-TD cases having marked increase in expression of histone genes (e.g., *HIST1H4F* and *HIST1H2B1*) and a subset of posterior *HOXB* cluster genes (e.g., *HOXB9).* Further inspection using UMAP (Uniform Manifold Approximation and Projection) of expression profiles across different pediatric AML cohorts revealed two unclassified cases of AML that clustered with the *UBTF*-TD subtype (**Figure 1**). One case had a *WT1*p.S364* and the other a somatic *GATA2 p.R338fs* and *FLT3*-ITD, but did not contain an exon 13 duplication or other defining alterations. Upon closer inspection of the *UBTF* gene in these cases, we uncovered that each case had an in-frame tandem duplication in exon 9 of *UBTF* encoding a region between HMG box 2 and 3 with features similar to those in exon 13 (**Figure 2**). We therefore postulated that exon 9 TDs (*UBTF*-e9) could represent a functionally equivalent subgroup of *UBTF*-TDalterations.

To test this hypothesis, cord-blood CD34+ (cbCD34+) cells were transduced to test the transforming potential of *UBTF*-e9 duplications. Like with UBTF-e13 duplications, cbCD34+ cells expressing UBTF-e9 duplications displayed increased proliferation compared to UBTF -WT and lentiviral empty vector control in liquid culture; and increased colony counts and replating capacity, increased CD117 expression, and a more blast-like morphology in CFU assays. Collectively, these data suggest that like TDs in exon 13, exon 9 TDs are also sufficient to promote leukemogenic phenotypes.

In conclusion, we find that *UBTF*-TDs occur in both MDS and AML and are associated with lower WBC count, myelodysplasia, and stem cell-related surface marker expression. We have also expanded the spectrum of *UBTF*alterations in myeloid neoplasms through the identification of rare *UBTF* duplications in exon 9 that induce a similar transcriptional signature to exon 13 *UBTF*-TDs. The recent identification of *UBTF*-TDs in adult and pediatric high-risk myeloid neoplasms has highlighted the importance of understanding and appropriately diagnosing tumors with this genomic alteration, including a new class of alterations that will not be detected by PCR-based screening strategies that specifically target exon 13 of *UBTF.*

Disclosures No relevant conflicts of interest to declare.

Figure 1. *UMAP of pediatric AML cohort (n = 939)*

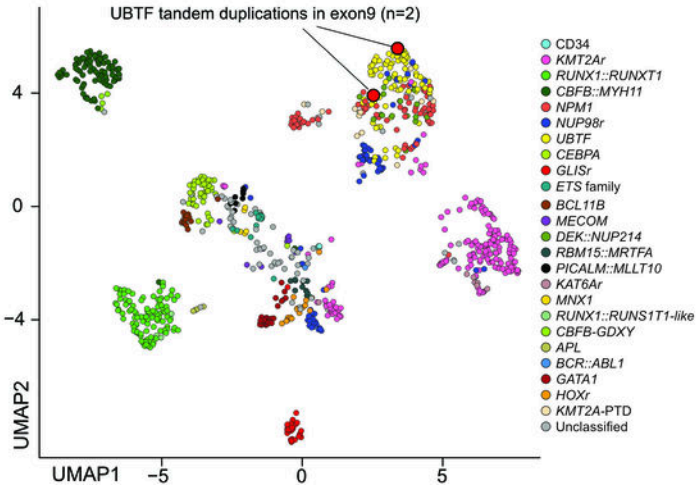

Figure 2. *Characterization of UBTF Exon 9 Tandem Duplications*

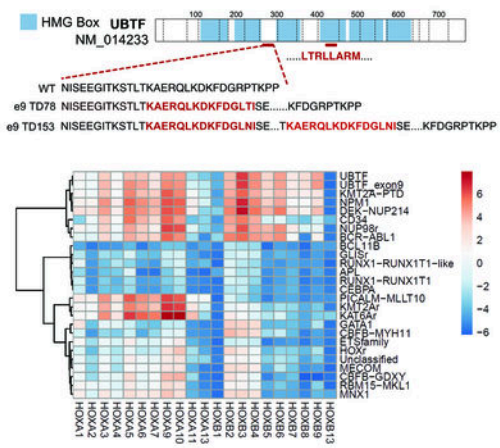

Figure 1

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