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POSTER ABSTRACTS

602.MYELOID ONCOGENESIS: BASIC

Integrative Genome and Transcriptome Sequencing Analysis Indicates Genetic and Epigenetic Dysregulation in DS-AML

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Down Syndrome related AML is driven by GATA1 alterations in patients with trisomy 21. Using exome or targeted sequencing, prior studies identified GATA1 alterations in ~80-90% of patients. We performed whole genome sequencing coupled with whole transcriptome sequencing on 207 cases to study the genomic basis of Down Syndrome AML. We detected GATA1 alterations in 96.1% of cases, with additional structural rearrangements in GATA1 in 15% of cases that may have been missed in prior studies. For GATA1, although substitutions and small indels occur nearly uniformly across exon 2, we observed that internal tandem duplications (ITDs) are significantly enriched in the second half of exon 2, suggesting a specific mutational mechanism for these cases. We also detected exon 3 (instead of exon 2) deletion in one case, where the resultant truncated GATA1 protein is different from the commonly recognized sGATA1. Our study further revealed that mutations in genes mediating JAK-STAT signaling (JAK1/JAK2/JAK3), RAS pathway (KRAS/NRAS/NF1), Cohesin complex (STAG2/CTCF/RAD21/SMC3), as well as MBNL1, KANSL1, IRX1, and NFIA. By integrating the genome with transcriptome sequencing data, we discovered that GATA1 exon 2 skipping to be a significant event in DS-AML. Although exon 2 is nearly completely skipped in cases with exon 2 deletion or splice site alterations, significant exon 2 skipping is also observed in cases where the alteration is small and is in the middle of exon 2. Further, exon 2 skipping is also observed in cases wither the alteration is a single base substitution that results in stop codon in the middle of exon 2 (therefore splicing is unlikely affected by these alterations in such cases). Based on this observation, we propose a hybrid genetic-epigenetic model on the development of Down Syndrome AML. In DS-AML, GATA1 exon 2 skipping during transcription/splicing might be a developmentally (epigenetically) regulated event in early fetal development that is destined to be silenced in the postnatal period that results in activation of the canonical long GATA1. This epigenetic silencing of sGATA1 is overridden by secondary genetic events, thus maintaining sGATA1 as the predominant GATA1 protein. Notably, the sGATA1 have variable isoforms as a result of exon 2 or exon 3 loss. In summary, our integrated whole genome and transcriptome approach has resulted in discovery of novel and high-prevalence structural alterations in GATA1 and potentially novel genes involved in pathogenesis of DS-AML. Our integrated analysis provided evidence on the epigenetic/developmental regulation of GATA1 exon 2 skipping via alterative splicing in the context of trisomy 21 that warrants further investigation.

Disclosures No relevant conflicts of interest to declare.

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