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Acute Leukemias

COMBINED *NF1/SUZ12* HAPLOINSUFFICIENCY DRIVES ABERRANT ACTIVATION OF THE RAS SIGNALING CASCADE IN IMMATURE *HOXA*-POSITIVE T-ALL

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Introduction: Deletions of the long arm of chromosome 17 (I-17q) in immature T-cell acute lymphoblastic leukemia (T-ALL) of adults encompass *NF1* and *SUZ12*. *NF1* encodes a negative regulator of the RAS pathway while *SUZ12*, a member of the PRC2 complex, is an epigenetic modulator that mediates the methylation of H3K27. Inactivation of *NF1* and *SUZ12* has been reported to synergistically enhance RAS/MAPK signaling in JMML and solid tumors (Zhang M, Nat Genet 2014; Caye A, Nat Genet 2015; de Raedt T, Nature 2014).

Aim: To elucidate the biological and functional impact of *NF1* and *SUZ12* haploinsufficiency in T-ALL.

Methods: The I-17q abnormality was detected in 39 out of 447 genomically characterized T-ALL cases (288 adults and 159 children) using a multimodal approach combining FISH, SNP array, and targeted custom NGS analyses. *SUZ12* knock down (*SUZ12*-KD) in the PF382-Cas9 cell line, which harbors an *NF1* loss-of-function mutation, was used to model concurrent *NF1* and *SUZ12* haploinsufficiency. Gene expression analysis was performed by Whole Transcriptome Expression array (WTEa) (Bardelli V, J Mol Diagn 2025) and qRT-PCR, while MAPK pathway activation was assessed by Western blot analysis of phosphorylated ERK (pERK).

Results: I-17q correlated with *NF1* and *SUZ12* haploinsufficiency and was restricted to the leukemic clone, disappearing upon hematologic and cytogenetic remission. It was significantly linked to adulthood (Chi-square, $p = 0.002$) and an immature phenotype ($p < 0.001$), and was enriched in cases with high *HOXA* expression levels (present in >40% of I-17q–-positive cases), which in 68% of cases were driven by known genomic alterations (3 *HOXA*, 3 *NUP214*, 2 *MLLT10*, 2 *ZFP36L2*, and 1 *KMT2A*). According to the immature phenotype, upregulation of *IGFBP7*, *MN1*, *CD34*, *MEF2C*, *RUNX2*, and *BAALC*, typically expressed in hematopoietic/progenitor cells, was observed. In addition, GSEA demonstrated enrichment of MAPK pathway signature. In vitro studies showed that the *NF1*-mutant PF382 cell line exhibited increased ERK phosphorylation after *SUZ12* knockdown. Furthermore, enhanced ERK phosphorylation was observed in primary I-17q samples, supporting a cooperative role of *NF1* and *SUZ12* loss.

Conclusions: I-17q marks immature T-ALL of adults with high levels of *HOXA* expression. Reflecting a model of concurrent *NF1/SUZ12* loss observed in other human tumors, our data indicate that *NF1* loss drives activation of the RAS/RAF/MEK/ERK pathway, which is further enhanced by *SUZ12* haploinsufficiency, highlighting this signaling cascade as a potential therapeutic target.