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A novel tripartite *STAT5B::RARA::RP11-750B16.1* fusion in variant acute promyelocytic leukemia. Comment on: "Novel ligand-binding domain truncated *CPSF7::RARA::CPSF7* tripartite fusion confers primary ATRA resistance in atypical acute promyelocytic leukemia"

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A novel tripartite *STAT5B::RARA::RP11-750B16.1* fusion in variant acute promyelocytic leukemia. Comment on: "Novel ligand-binding domain truncated *CPSF7::RARA::CPSF7* tripartite fusion confers primary ATRA resistance in atypical acute promyelocytic leukemia"

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The recent discovery of tripartite *RARA* and *RARG* fusion genes has fundamentally reshaped our understanding of ATRA resistance in atypical acute promyelocytic leukemia (aAPL). Dong et al. recently reported a novel *CPSF7::RARA::CPSF7* tripartite fusion in a case of aAPL with primary resistance to all-trans retinoic acid (ATRA). By whole-transcriptome sequencing, the authors identified an in-frame fusion linking *CPSF7* exons 1–5 to RARA exons 3–8, followed by *CPSF7* exons 6–9. This tripartite configuration resulted in deletion of *RARA* exon 9 and consequent truncation of the ligand-binding domain (LBD) helix 11–12 (H11_12), which was functionally validated to confer complete ATRA unresponsiveness.[1] Recently, we identified a novel *STAT5B::RARA::RP11-750B16.1* tripartite fusion in an aAPL patient. Our discovery may further broaden the molecular spectrum of tripartite RARA rearrangements.

The detailed clinical characteristics of this patient have been previously described in our prior report.[2] In general, a 59-year-old female presented with nausea and vomiting. Laboratory evaluation revealed a white blood cell count of 7.69×10^9/L, hemoglobin 101 g/L, and platelet count 189×10^9/L. Bone marrow aspiration demonstrated 86% abnormal promyelocytes, with positivity for myeloperoxidase and $CD33^{++}/CD13^{+}$ by flow cytometry. Chromosomal analysis showed a normal karyotype. PCR testing confirmed the presence of the *STAT5B::RARA* fusion gene. The patient was diagnosed with variant APL but unfortunately passed away on day 23 of hospitalization during induction chemotherapy.

Transcriptome sequencing performed on the diagnostic bone marrow sample identified a novel tripartite fusion transcript, *STAT5B::RARA::RP11-750B16.1*. At the first fusion junction, exon 15 of *STAT5B* was fused in-frame with exon 3 of *RARA*. Downstream of *RARA* exon 9, the native sequence was replaced by a segment derived from *RP11-750B16.1*, a processed pseudogene. This fusion was verified through RT-PCR and Sanger sequencing.

Recent studies have unveiled a novel class of tripartite *RARA* and *RARG* fusions in variant APL. Unlike the classical bipartite *PML::RARA* fusion, these rearrangements involve not only a 5′ partner gene fused to *RARA* or *RARG*, but also an additional 3′ partner sequence. In *STAT5B::RARA*-positive cases, the 3′ portion of *RARA* has been shown to fuse with transposable elements (TEs) such as *AluSx4*, *MIRb-AluSc*, *HUMUT5218*, and *AluJo*, resulting in truncation of the ligand-binding domain (LBD) helices 11–12 and consequent resistance to ATRA.[3] Our identification of *RP11-750B16.1* as the 3′ fusion partner represents the first documented involvement of a pseudogene.

RP11-750B16.1 (ENSG00000262902) is a processed pseudogene located on chromosome 17q22. It comprises a single exon with a transcript length of 625 bp. Processed pseudogenes are derived from retrotransposition of mature mRNAs and typically lack introns and regulatory elements; they have traditionally been considered non-functional genomic fossils.[4] However, emerging evidence suggests that pseudogenes can regulate their parental genes through diverse mechanisms, including competing endogenous RNA networks and epigenetic modulation.[5,6] Interestingly, a recent transcriptomic study in allergic patients identified *RP11-750B16.1* among the top 50 differentially expressed non-coding transcripts in B cells, with a $\log_2$ fold change of 1.29 ($p = 0.014$),[7] indicating that this pseudogene is transcriptionally active in hematopoietic cells. Its ability to be transcribed and incorporated into a fusion transcript further supports its potential functional relevance.

In *STAT5B::RARA* tripartite fusions, the 3′ splice consistently truncates the *RARA* LBD within the H11–H12 coding region. In our case, fusion with *RP11-750B16.1* results in replacement of the native *RARA* 3′ end, likely leading to loss of the H12 helix. This truncation abolishes the allosteric transition required for coactivator recruitment upon ATRA binding, thereby explaining the clinical resistance to ATRA observed in this patient and in previously reported *STAT5B::RARA*-positive cases.[3,8] Notably, while transposable elements are the most frequently identified 3′ partners in *STAT5B::RARA* tripartite fusions, our finding demonstrates that non-TE sequences—specifically, a transcribed pseudogene—can also serve this function. This expands the repertoire of potential 3′ fusion partners and suggests that any sequence conferring a polyadenylation signal and capable of being transcribed in cis may participate in tripartite fusion formation.

The rarity of variant APL and the diversity of *RARA* fusion partners have long hindered mechanistic understanding. The discovery of tripartite fusions provides a unifying explanation for ATRA resistance in a subset of these cases.[3] Our report adds to this framework by introducing pseudogene-derived sequences as a novel class of 3′ fusion partners. It remains to be determined whether *RP11-750B16.1* contributes additional functions beyond providing a termination signal, such as affecting transcript stability or mediating interactions with regulatory RNAs.

In conclusion, we describe the first case of variant APL harboring a tripartite *STAT5B::RARA::RP11-750B16.1* fusion. This finding expands the known landscape of RARA rearrangements and highlights the potential involvement of pseudogenes in the pathogenesis of rare hematologic malignancies.

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