haematologica
Journal of the Ferrata Storti Foundation

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Received: December 10, 2025.
Accepted: March 5, 2026.

Citation: Zhan Su and Xin Liu. Comment on "Acute Promyelocytic Leukemia with other RARA rearrangements"
Haematologica. 2026 Mar 12. doi: 10.3324/haematol.2025.300363 [Epub ahead of print]

Comment on "Acute Promyelocytic Leukemia with other *RARA* rearrangements"

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Key words
RARs, fusion gene, acute promyelocytic leukemia

Acknowledgments and Funding Nil.

Conflict of interest The authors declare no competing interests.

Author contributions Zhan Su and Xin Liu designed the study and drafted the manuscript. All authors read and approved the final manuscript.

The International Consensus Classification (ICC) of acute myeloid leukemia has expanded the classification of Acute Promyelocytic Leukemia (APL) by introducing a new subtype termed "Acute Promyelocytic Leukemia with other *RARA* rearrangements." However, the current nomenclature may not be fully representative, as it does not explicitly encompass variant APL harboring RARB/RARG rearrangements. We therefore propose revising the name to "APL with other *RAR* rearrangements" to more accurately reflect the molecular pathology. Further subcategorization based on ATRA responsiveness may also be considered.

Acute Promyelocytic Leukemia (APL) is one of the most extensively researched and deeply understood subtypes of acute myeloid leukemia, and also the one with the most remarkable treatment outcomes. Its most common molecular pathological feature is the formation of a fusion gene involving *RARA* and a partner gene. Among these, *PML::RARA* (the classic type) accounts for 95%-98% of cases, while the remainder involve partner genes other than *PML* (variant types). To date, more than twenty variant *RARA*-related fusion genes have been identified, with new ones being reported annually. In recent years, a novel fusion —*TTMV::RARA*— has been identified, resulting from the insertion of Torque Teno Mini Virus (TTMV) sequences into the *RARA* gene. This subtype demonstrates distinct clinicopathological and molecular features.[1]

However, there exists another category of acute myeloid leukemia that resembles APL in its morphology, cytochemistry, and immunophenotype, but lacks *RARA* gene abnormalities. Some researchers refer to this leukemia as acute promyelocytic-like leukemia (APLL). Some authors classify it as AML-M2, while others categorize it as having monocytic differentiation (FAB classification). For many years, the molecular biological abnormalities underlying APLL remained unclear.

Retinoic acid receptors (RARs) are a subfamily within the Nuclear Receptor Superfamily, comprising three subtypes: RARA, RARB, and RARG. These three subtypes are highly conserved evolutionarily, with highly similar sequences and functions. Therefore, given the identification of X-*RARA* fusion genes in most APL cases, researchers previously hypothesized that *RARB* and *RARG* might play important roles in APLL. Entering the 21st century, with technological advancements, various high-throughput detection techniques have emerged as powerful tools for genomic research, leading to the discovery of genetic abnormalities in many diseases. In recent years, driver gene mutations in some APLL cases have been successively reported. As early as 2011, Such et al. identified a *NUP98::RARG* fusion gene in a Spanish patient.[2] Subsequently, several fusion genes involving *RARG* were identified. In 2017, a *PML::RARG* fusion gene was discovered in a Korean patient.[3] In 2018, Professor Suning Chen and Professor Honghu Zhu, among others, respectively reported the *CPSF6::RARG* fusion gene[4,5], while Miller et al. identified its reciprocal fusion gene, *RARG::CPSF6.*[6] We also first identified the *HNRNPC::RARG* fusion gene in an APLL case.[7] *NPM1::RARG::NPM1* was reported by Chen et al..[8] These findings suggest that *RARG* gene rearrangements exist in some APLL cases. Osumi et al. discovered a *TBLR1::RARB* fusion gene in a Japanese patient.[9] Thus, recurrent *RARB* and *RARG* fusion genes have been identified in APLL, validating previous researchers' hypotheses. In recent years, more cases have been progressively identified, with some reported in publications. After 2022, *RARG::HNRNPM*, *SART3::RARG*, *PRPF19::RARG*, as well as *FNDC3B::RARB* and *HNRNPC::RARB* have been identified[10–14].

In November 2021, the "International Consortium on *RARG*-rearranged Acute Myeloid Leukemia" was established, bringing together the lead authors of all then-published articles on *RARG* fusion genes, as well as researchers with unpublished cases. This consortium is dedicated to the discovery and recording of cases of this disease, summarizing its clinical characteristics, exploring its pathogenesis, and investigating treatment methods.[15] The consortium proposed that *RARG*-rearranged AML could be a candidate category of AML, parallel to *RARA*-rearranged APL.

A substantial proportion of variant APL cases — including a minority of those with *RARA* rearrangements and the vast majority of those with *RARG* or *RARB* rearrangements — do not respond to treatment with all-trans retinoic acid (ATRA) and/or arsenic trioxide (ATO), and the underlying mechanism has long been unclear. Recently, a significant breakthrough revealed the molecular mechanism. The study found that in some cases carrying *RARA* rearrangements and all cases with *RARG* rearrangements (atypical APL, aAPL), a novel three-part fusion gene structure exists, in the form of *X::RAR::X* or *X::RAR::Y*. This fusion event involves not only a 5' fusion partner of the *RARA* or *RARG* gene but also introduces an additional 3' fusion partner. Notably, during this fusion process, the ligand-binding domain (LBD) of RARA and RARG – specifically the helix 11-12 and H12 domains – undergoes truncating mutations. This results in chimeric proteins that cannot effectively bind ATRA, thereby losing the ability to activate target genes via the ligand, mediating resistance to ATRA therapy.[16] However, the tripartite fusion model does not account for all cases of ATRA-resistant variant APL — for example, those harboring *ZBTB16::RARA*.

In previous editions of the WHO classification of hematopoietic and lymphoid tumors, APL was represented by only one entity: "APL with *PML::RARA*" while variant APL was overlooked. This narrow focus was intended to emphasize both the favorable response of classic APL to ATRA and its overwhelming predominance in case numbers compared to variant APL. This gap should be addressed, as the diagnosis of variant APL is becoming more frequent. Indeed, our review of early reported APLL cases with undefined molecular mechanisms revealed that some harbored chromosomal abnormalities linked to *RARG* rearrangements. Moreover, a considerable proportion of these cases are resistant to ATRA, underscoring the need for early confirmation at initial diagnosis to guide appropriate treatment decisions. It is encouraging that the fifth edition of the WHO classification has included "*RARG*-rearranged AML," placing it under "other rare fusions" within the category of "AML with other defined genetic alterations." However, the updated WHO classification does not refer to *RARB*-rearranged APL.

In 2022, the International Consensus Classification (ICC) of hematolymphoid tumors was also released. The ICC brought groundbreaking changes to the classification of APL. In the ICC, APL is divided into two subtypes. The first is classic APL, and the second is a newly added type, namely "APL with other *RARA* rearrangements." This second subtype includes *RARA*-related fusion genes other than *PML::RARA*. The ICC also notes that rare cases involving other RAR family genes have been reported.[17] With the growing number of documented *RARB/RARG*-rearranged APL cases, we believe it is reasonable to include them under this second subtype . "*RARs*" is the collective term for the retinoic acid receptor family. Using it to name the second APL subtype would be most appropriate, i.e., "APL with other *RAR* rearrangements."

Furthermore, given the marked heterogeneity of variant APL, merely listing it as a single entity offers limited value, and further subtyping should be considered. We have contemplated classifying based on response to ATRA therapy (sensitive vs. resistant) due to its direct clinical relevance. However, this approach has notable limitations: many patients receive combination therapy including ATRA, ATO, and chemotherapy, making it difficult to attribute treatment outcomes solely to ATRA; additionally, early relapse in some patients who initially achieve remission complicates the practical definition of "sensitivity." Another possible method is to subclassify according to the specific retinoic acid receptor gene involved (*RARA*, *RARB*, and *RARG*). The main limitation of this framework is its inability to directly guide clinical decision-making. Further discussion is needed to develop a more comprehensive and nuanced subtyping system.

Finally, we thank the editorial boards of the ICC and WHO classifications. We hope that future revisions of these classifications may consider adopting the more comprehensive concept of "APL with other RAR rearrangements".

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