

## Leukaemia Section

### Short Communication

# t(1;17)(p34;q21) IRF2BP2/RARA

Adriana Zamecnikova

Kuwait Cancer control Center, Department of Hematology, Kuwait; annadria@yahoo.com

Published in Atlas Database: March 2017

Online updated version : <http://AtlasGeneticsOncology.org/Anomalies/t0117p34q21ID1603.html>

Printable original version : <http://documents.irevues.inist.fr/bitstream/handle/2042/68763/03-2017-t0117p34q21ID1603.pdf>

DOI: 10.4267/2042/68763

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.  
© 2018 Atlas of Genetics and Cytogenetics in Oncology and Haematology

### Abstract

Acute promyelocytic leukemia (APL) is characterized by the clonal expansion of myeloid precursors blocked at promyelocytic stage and the presence of t(15;17)(q24;q21) resulting in the fusion of retinoic acid receptor alpha (RARA) gene on 17q21.1 with promyelocytic leukemia (PML) gene at 15q24.1, and less frequently with other gene partners. Fusion between RARA and the interferon regulatory factor 2 binding protein 2 (IRF2BP2) genes is a rare variant translocation in APL.

#### KEYWORDS

Chromosome 1; chromosome 17; acute promyelocytic leukemia; all-trans retinoic acid, RARA fusion genes; interferon regulatory protein 2 binding protein 2; IRF2BP2; IRF2BP2/RARA

### Clinics and pathology

#### Disease

Acute promyelocytic leukemia (APL; FAB type M3)

#### Epidemiology

Only 3 cases to date, 2 females aged 19 and 68 years (Yin et al., 2015; Shimomura et al., 2016) and a 37-years old male patient (Jovanovic et al., 2017).

#### Clinics

The 68-year-old female presented with no disseminated intravascular coagulation (DIC) Bone marrow showed marked hypercellularity with 36.8% promyelocytes with azurophilic granules and Auer rods. Immunophenotyping was positive for CD33, CD34, CD64, CD117 and HLA-DR (Shimomura et al., 2016).

#### Prognosis

The 19-year-old woman received all-trans retinoic acid (ATRA), arsenic trioxide and gemtuzumab ozogamicin and achieved complete remission but relapsed 10 months later (Yin et al., 2015). The other female patient received induction therapy with ATRA in combination with chemotherapy. After initial resistance she achieved hematological remission after re-induction therapy and remained in hematological remission for more than a year when she developed relapse and died 1 year later (Shimomura et al., 2016). The male patient was commenced on ATRA as a single agent and showed response to therapy revealing maturation of the leukemic blasts in bone marrows taken at day 7 and day 16 that was associated with normalization of the platelet count. Because real-time quantitative PCR showed persistent high level IRF2BP2/RARA fusion transcripts with ATRA as a single agent, chemotherapy was added that resulted in ongoing

remission 32 months from diagnosis (Jovanovic et al., 2017).

## Cytogenetics

### Cytogenetics molecular

Cryptic rearrangement, detected by next-generation RNA-sequencing analysis followed by RT-PCR and direct sequencing in 1 (Yin et al., 2015), a paired-end mRNA sequencing followed by RT-PCR and direct sequencing in 1 (Shimamura et al., 2015) and 5' RACE-PCR in 1 case (Jovanovic et al., 2017).

## Genes involved and proteins

### ***IRF2BP2 (interferon regulatory factor 2 binding protein 2)***

#### Location

1q42.3

#### Protein

Belongs to a family of proteins that play a major role in the transcriptional regulation; acts as a transcriptional corepressor binding to the C-terminal repression domain of IRF2, a negative regulator of many interferon-responsive genes; its C-terminal RING-type zinc finger domain is sufficient for interaction with IRF2; this repression is not mediated by histone deacetylase activities.

### ***RARA (Retinoic acid receptor, alpha)***

#### Location

17q21.2

#### Protein

Nuclear retinoic acid receptor; belongs to the large family of ligand responsive gene regulatory proteins, function as heterodimers with retinoid X receptors.

## Result of the chromosomal anomaly

### Hybrid gene

#### Transcript

5' IRF2BP2 - 3' RARA.

In the case reported by Yin et al., 2015, breakpoints within IRF2BP2 exon 2 and RARA intron 2 were detected with breakpoints at positions 1687 bp in IRF2BP2 and 41620 bp in RARA. Through alternative splicing, 2 types of fusion transcripts

between exon 1B of IRF2BP2 and exon 3 of RARA that resulted in an mRNA transcript 48 bp longer than variant 2 were found in a patient described by Shimomura et al., 2016. In the recently described case, fusion of exon 1 of IRF2BP2 to exon 3 of RARA was found (Jovanovic et al., 2017).

### Fusion protein

#### Description

The N terminal part of the fusion protein originates from IRF2BP2 harbouring a zinc finger motif which may bind DNA and the C terminal part contains regions mediating DNA binding, ligand binding and RXR heterodimerization (Shimomura et al., 2015; Jovanovic et al., 2017).

#### Oncogenesis

The cryptic IRF2BP2/RARA fusion shows a similar breakpoint within the RARA gene as in PML-RARA and variant RARA fusions, thus retaining DNA binding, RXR heterodimerization, ligand binding, and co-repressor and co-activator interaction functions of RARA. The IRF2BP2/RARA fusion protein is likely the central leukemia-initiating event in APL patients by transforming hematopoietic stem/progenitor cells. In co-immunoprecipitation assays, IRF2BP2/RARA had the capacity to self-associate and behaved similarly to PML/RARA, inducing repression at retinoid response elements (Jovanovic et al., 2017).

## References

- Jovanovic JV, Chillón MC, Vincent-Fabert C, Dillon R, Voisset E, Gutiérrez NC, Sanz RG, Lopez AA, Morgan YG, Lok J, Solomon E, Duprez E, Díaz MG, Grimwade D. The cryptic IRF2BP2-RARA fusion transforms hematopoietic stem/progenitor cells and induces retinoid-sensitive acute promyelocytic leukemia. *Leukemia*. 2017 Mar;31(3):747-751
- Shimomura Y, Mitsui H, Yamashita Y, Kamae T, Kanai A, Matsui H, Ishibashi T, Tanimura A, Shibayama H, Oritani K, Kuyama J, Kanakura Y. New variant of acute promyelocytic leukemia with IRF2BP2-RARA fusion. *Cancer Sci*. 2016 Aug;107(8):1165-8
- Yin CC, Jain N, Mehrotra M, Zhagn J, Protopopov A, Zuo Z, Pemmaraju N, DiNardo C, Hirsch-Ginsberg C, Wang SA, Medeiros LJ, Chin L, Patel KP, Ravandi F, Futreal A, Bueso-Ramos CE. Identification of a novel fusion gene, IRF2BP2-RARA, in acute promyelocytic leukemia. *J Natl Compr Canc Netw*. 2015 Jan;13(1):19-22

*This article should be referenced as such:*

Zamecnikova A t(1;17)(p34;q21) IRF2BP2/RARA *Atlas Genet Cytogenet Oncol Haematol*. 2018; 22(2) : 66-67.