t(7;17)(q11;q21) GTF2I/RARA in APL

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Abstract

Review on t(7;17)(q11;q21) GTF2I/RARA in acute promyelocytic leukaemia, with data on clinics, and the genes involved.

Keywords
acute promyelocytic leukaemia; GTF2I; RARA; t(7;17)(q11;q21)

Identity

Other names
cryptic t(7;17)(q11;q21) GTF2I/RARA in acute promyelocytic leukaemia (APL)

Disease
variant acute promyelocytic leukemia with ATRA resistance

Phenotype/cell stem origin
HLA-DR-, CD34-, CD13+, CD33+, CD64+

Epidemiology
One case reported so far. A 35-year old male.

Clinics
The patient exhibited leukocytosis and coagulopathy.

Cytology
The cytoplasm was occupied by densely packed coarse granules.
The nuclei were relatively regular. Auer rods and fagot cells were absent. MPO staining is strongly positive.

G-banding karyotype of del(7q). No distinct chromosome tranlocation.
Morphology of GTF2I-RARA variant APL. Wright Giemsa staining. Image acquired at x1000 magnification.

Metaphase fluorescence in situ hybridization (FISH). On the left, PML-RARA dual colour, dual-fusion translocation probes found RARA rearrangement. The RARA signals are shown in red, while PML signals are shown in green. Intact RARA and PML are shown as (r) and (p), while the split RARA signals are indicated as (s). In the middle, probes specific for the chromosome 7 centromere (GLP D7S486 probes, green) and 7q31 (CSP7 probes, red) confirmed the deletion of the long arm of one chromosome 7. On the right, the combined application of chromosome 7 probes and PML-RARA probes found that one split RARA was translocated to the truncated long arm of chromosome 7. Signal detection was carried out on metaphases according to the manufacturers protocols (Jinpujia, Beijing, China).

Schematic diagram of RARA, GTF2I and GTF2I-RARA fusion protein. A black line indicates the break point. DBD, DNA-binding domain; LBD + DD, ligand-binding domain and dimerization domain; LZ, leucine zipper; NLS, nuclear localization signal; BR, basic region; R1-R6, l-repeat domains.
Treatment
ATRA in combination with anthracycline-based chemotherapy did not induce remission. Neither are conventional chemotherapy and ATRA in combination with arsenics. No morphology differentiation of blast cells was seen after ATRA treatment.

Evolution
No remission was obtained after ATRA and conventional chemotherapy. The patient died of intracranial hemorrhage on day 143 without remission.

Prognosis
Bad.

Cytogenetics
Note
Cryptic translocation. FISH studies are needed to uncover the rearrangement.

Genes involved and proteins

GTF2I
Location
7q11
Note
General transcription factor Ii
Protein
GTF2I is a ubiquitously expressed phosphoprotein with broad roles in transcription and signal transduction involving growth factor signalling, cell cycle regulation, and transforming growth factor, beta 1 (TGFB1) signalling, ER stress response pathway, calcium signalling, and immune signalling (Roy, 2012).

RARA
Location
17q21
Note
Retinoic acid receptor alpha
Protein
RARA is a nuclear retinoic acid receptor that regulates transcription in a ligand-dependent manner. This gene has been implicated in regulation of hemopoietic cells differentiation.

Result of the chromosomal anomaly

Hybrid gene
Note
In-frame fusion of exon 6 of GTF2I to exon 3 of RARA

Transcript
5’GTF2I-3’RARA. No reciprocal 5’RARA-3’GTF2I.

Detection
Reverse transcript polymerase chain reaction.

Fusion protein
Description
The fusion transcript encodes a 598 amino acids chimera containing the 195 amino-terminal amino acids of GTF2I, including the N-terminal leucine zipper and the first I-repeat domain, and 403 carboxyl-terminal amino acids of RARA, including the DNA and ligand binding domains.

Expression / Localisation
Two patterns of GTF2I-RARA localization were observed: diffuse nuclear distribution with a micropunctate pattern, and aggregation in the cytoplasm as macrogranules.

Oncogenesis
GTF2I-RARA chimera possesses common features of APL related fusion proteins: the same RARA portion, the ability to self-associate, dominant-negative regulation of the retinoic acid response element, and aberrant subcellular localization.

References

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