

Leukaemia Section

Short Communication

t(14;19)(q32;q13) IGH/Various Partners

Jean Loup Huret

jean-loup.huret@atlasgeneticsoncology.org

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Abstract

Review on the various t(14;19)(q32;q13), with data on clinics, and the genes involved.

Keywords

Chromosome 14; chromosome 19; IGH; BCL3; CEBPA; CEBPG; ERF; FOSB; NECTIN2; PPP1R15A; SPIB; chronic lymphocytic leukemia; nodal marginal zone B-cell lymphoma; mature B-cell neoplasm; diffuse large B-cell lymphoma; splenic marginal zone B-cell lymphoma; follicular lymphoma; bilineage leukemia; Burkitt lymphoma; chronic myeloid leukemia; lymphoplasmacytic lymphoma; mantle cell lymphoma; Hodgkin disease, multiple myeloma.

Clinics and pathology

Disease

According to a search in Mitelman database "Cases Quick Searcher", 181 cases of t(14;19)(q32;q13) are available in the literature: 104 chronic lymphocytic leukemia cases (CLL), 30 acute B-cell lymphoblastic leukemia, 13 nodal marginal zone B-cell lymphoma, 12 mature B-cell neoplasm not otherwise specified (NOS), 10 diffuse large B-cell lymphoma, 5 splenic marginal zone B-cell lymphoma, 2 follicular lymphoma, 1 bilineage leukemia, 1 Burkitt lymphoma, 1 chronic myeloid leukemia, 1 lymphoplasmacytic lymphoma, and 1 mantle cell lymphoma.

A t(14;19)(q32;q13) IGH/BCL3 has been found in chronic lymphocytic leukemia, mature B-cell neoplasm NOS, diffuse large B-cell lymphoma, bilineage leukemia, follicular lymphoma, Hodgkin disease, nodal marginal zone B-cell lymphoma, and splenic marginal zone B-cell lymphoma.

A t(14;19)(q32;q13) IGH/CEBPA or CEBPG, but also other translocations with IGH fused to CCAAT/enhancer binding proteins (CEBPB (20q13), CEBPD (8p11), CEBPE (14q11)) has been found so far only in acute B-cell lymphoblastic leukemia.

Other t(14;19)(q32;q13) with IGH involvement have been found in multiple myeloma (IGH/ERF, IGH/FOSB, IGH/PPP1R15A (Cleyne et al., 2017)) and diffuse large B-cell lymphoma (IGH/NECTIN2, IGH/SPIB (Lenz et al 2007; Otto et al., 2016)).

Cytogenetics

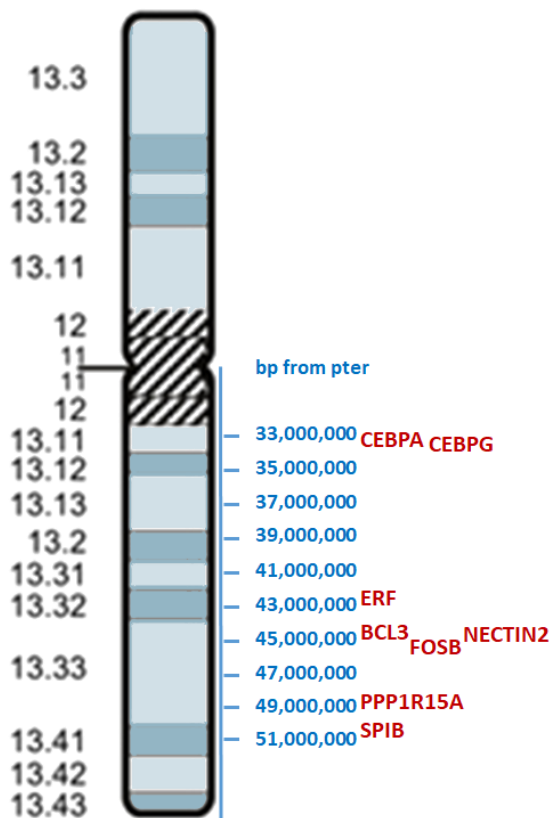
t(14;19)(q32;q13) IGH/BCL3
t(14;19)(q32;q13) IGH/CEBPA or CEBPG
t(14;19)(q32;q13) IGH/ERF
t(14;19)(q32;q13) IGH/FOSB
t(14;19)(q32;q13) IGH/NECTIN2
t(14;19)(q32;q13) IGH/PPP1R15A
t(14;19)(q32;q13) IGH/SPIB

Cytogenetics

Cytogenetics morphological

IGH partners in the t(14;19)(q32;q13)

Gene	Chrom. Band	Starts-Ends (from pter)
CEBPA	19q13.11	33,299,934 - 33,302,564
CEBPG	19q13.11	33,373,669 - 33,382,686
ERF	19q13.2	42,247,561 - 42,255,164
BCL3	19q13.32	44,748,721 - 44,760,044
NECTIN2	19q13.32	44,846,136 - 44,878,941
FOSB	19q13.32	45,467,995 - 45,475,179
PPP1R15A	19q13.33	48,872,392 - 48,876,062
SPIB	19q13.33	50,418,938 - 50,431,052



Genes involved and proteins

IGH (immunoglobulin heavy locus)

Location 14q32.33

BCL3 (BCL3 transcription coactivator)

Location 19q13.32

Starts at 44748721 and ends at 44760044 bp from pter.

Protein

454 amino acids (aa). BCL3 contains seven ankyrin repeats (aa 134-163, 171-200, 204-235, 241-270, 275-304, 308-337, 338-367). BCL3 is a member of the I-kappaB family (NFKBIA (NFKB inhibitor alpha), NFKBIB (NFKB inhibitor beta) and others), whose proteins regulate the NF-kB family of transcription factors. BCL3 interacts with NFKB1 and NFKB2 (NF-kappaB p50 and p52). NF-kB plays a major role in B-cell development. BCL3 is induced by LIF and plays a role in the maintenance of pluripotency. BCL3 stimulates cell-cycle progression in a breast cancer cell line. BCL3 interacts with TRAF6. The ankyrin repeats of BCL3 bind the RING domain of TRAF6. TRAF6 mediate a NF-kB signaling via BCL3 to promote osteoclastogenesis (Otsuka et al., 2018; Wang et al., 2018)

CEBPA (CCAAT/enhancer binding protein (C/EBP), alpha)

Location 19q13.11

Starts at 33299934 and ends at 33302564 bp from pter.

Protein

358 amino acids. CEBPA contains a bzip (aa 282-345, with a basic motif (aa 286-313) and a leucine zipper (aa 317-345)). Transcription factor. Binds the consensus DNA sequence T[TG]NNGNAA[TG] as a homo or heterodimer. Key factor driving myeloid cell differentiation of hematopoietic stem cells and also driving differentiation of other cell lineages (Tian and Graf, 2014).

CEBPG (CCAAT enhancer binding protein gamma)

Location 19q13.11

Starts at 33373669 and ends at 33382686 bp from pter. CEBPG is located only 71 kb distal of CEBPA.

Protein

150 amino acids. CEBPG contains a bzip (aa 62-125, with a basic motif (aa 66-93) and a leucine zipper (aa 97-118)).

Transcription factor. CEBPG homodimers are cytostatic and promote cell cycle arrest and senescence. Conversely, CEBPB/CEBPG heterodimers display reduced transcriptional potential. However, CEBPG deletion did not alter hematopoietic stem and progenitor cell ability to commit to the myeloid lineage. ATF4/CEBPG heterodimer is an antioxidant regulator that controls redox homeostasis in normal and cancerous cells. CEBPG acts as a negative regulator of senescence and promotes proliferation of multiple cell types (Huggins et al., 2013; Huggins et al., 2015; Kardosova et al., 2018).

ERF (ETS2 repressor factor)

Location 19q13.2

Starts at 42247561 and ends at 42255164 bp from pter.

Protein

548 amino acids. ERF contains an ETS domain (aa 29-106), an ERK interaction domain (aa 294-385), and a repressor domain (aa 472-530). Member of the ETS family of transcription factors. ERF translocates to the nucleus, where it binds to enhancers of RAS targets, pluripotency and mitogenic factors. ERF may play a role in limiting mouse embryonic stem cells differentiation. Loss-of-function ERF germline mutations are implicated in an autosomal form of craniosynostosis (Mayor-Ruiz et al., 2018).

FOSB (FosB proto-oncogene, AP-1 transcription factor subunit)**Location** 19q13.32

Starts at 45467995 and ends at 45475179 bp from pter.

FOSB is also called AP-1 (which is confusing with the "AP-1 complex").

Protein

338 amino acids. FOSB contains a bzip (aa 155-218, with a basic motif (aa 157-182) and a leucine zipper (aa 183-211)). Transcription factor, member of the AP-1 Transcription Factors family: AP-1 complex is a dimeric complex composed of members from the JUN, FOS (FOS, FOSB, FOSL1 and FOSL2 (FRA-1 and FRA-2)), ATF, or MAF protein families. The sequence elements to which AP-1 transcription factors bind differ depending on the distinctive homo- or hetero-dimer combinations. FOS proteins bind the TRE sequence: TGACTCA. FOS proteins only form hetero-dimers (review in Garces de Los Fayos Alonso et al., 2018).

ΔFosB, a splice variant of FOSB is induced by stress, antidepressants, and drugs abuse in brain regions such as the prefrontal cortex and the hippocampus (Palafox-Sanchez et al., 2019).

NECTIN2 (nectin cell adhesion molecule 2)**Location** 19q13.32

Starts at 44846136 and ends at 44878941 bp from pter.

NECTIN2 is also called PVRL2 (poliovirus receptor-related 2).

Protein

NECTIN2 is a cell membrane protein involved in immune checkpoint, part of the TIGIT-PVR/PVRL2 axis. NECTIN2 is composed of a signal peptide (amino acids 1-31), an extracellular domain (aa 32-360), a transmembrane domain (aa 361-381), and a cytoplasmic domain (aa 382-538). NECTIN2 also interacts with PVRIG CD226, CD96 to stimulate or inhibit lymphocyte cell signaling (Stamm et al., 2018; Whelan et al., 2019).

PPP1R15A (protein phosphatase 1 regulatory subunit 15A)**Location** 19q13.33

Starts at 48872392 and ends at 48876062 bp from pter

PPP1R15A is also called GADD34.

Protein

674 amino acids. PPP1R15A inhibits the proteasomal degradation of MCL1 and enhances MCL1 protein stability. PPP1R15A overexpression promotes MAPK signaling pathway through TRAF6 and TAB1, which mediates the up-regulation of MCL1 (Song et al., 2019).

SPIB (Spi-B transcription factor)**Location** 19q13.33

Starts at 50418938 and ends at 50431052 bp from pter.

Protein

262 amino acids. SPIB contains two transactivation domains (aa 1-31 and 41-61). Binds to the nucleotide sequence GGAA. Transcriptional activator of B-cell development and differentiation. SPI1 (spleen focus forming virus (SFFV) proviral integration oncogene spi1, also known as PU.1) and SPIB control many components of the B-cell receptor (BCR) pathway. SPI1 and SPIB are partially redundant. Inactivation of SPI1 and SPIB in B-cell progenitors blocks the development at the pre-B-cell stage and induces pre-B acute lymphoblastic leukemia. Inactivation SPI1 and SPIB in mature B cells prevents germinal centers development. SPI1 and SPIB negatively regulate plasma cell differentiation (Willis et al., 2017).

Result of the chromosomal anomaly**Hybrid gene****Description**

CEBPA and CEBPG cases: The breakpoints clustered within the 3' UTR of CEBPA in most cases, and was 31 kb centromeric of CEBPA in one case. The breakpoint was 52 kb centromeric of CEBPG (Akasaka et al., 2007). NECTIN2 case: The breakpoint in NECTIN2 was located in exon 1 in the 5'untranslated region at position 45,349,458 from the p terminus of chromosome 19 (Otto et al., 2016).

Fusion protein**Oncogenesis**

In the case reported by Otto et al., 2016, NECTIN2 was expressed at a significantly higher level than in the other 363 DLBCL studied.

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