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Review

t(2;18)(p11;q21) IGK/BCL2 and IGK/KDSR

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Abstract

Review on t(2;18)(p11;q21)IGK/BCL2 and IGK/KDSR, and the dual role of the neighbor genes BCL2 and KDSR

KEYWORDS

Chromosome 2; chromosome 18; IGK; KDSR; Follicular lymphoma; Diffuse large B-cell lymphoma; Burkitt lymphoma; Chronic lymphocytic leukemia

Identity

t(2;18)(p11;q21) is a very rare reciprocal translocation described only in a 13 cases with B-lymphoproliferative disorders mainly follicular lymphomas (FL). The anomaly represents a minor variant of the classical t(14;18)(q32;q21) which is the most frequent translocation associated with follicular lymphoma (FL). In contrast to t(14;18) that juxtapose BCL2 with the heavy chain locus, t(2;18) resulted to the juxtaposition of the BCL2 to the kappa light chain locus. Despite of this difference the consequence of t(2;18) is the same as that in t(14;18) - deregulation of BCL2 leading to inhibition of apoptosis and respectively accumulation of a long living B-cells. A molecular variant of t(2;18)(p11;q21), in which the kappa light chain instead with BCL2 is rearranged with the coding region termed FVT-1 (for follicular lymphoma variant translocation - IGK/FVT-1), is also described Rimokh et al. (1993). It was ascertained later that FVT-1 coded the gene of 3-ketodihydroshingosine reductase (KDSR) - a key enzyme in the "de novo" synthetic pathway of ceramide.

Clinics and pathology

Disease

Follicular lymphoma

Phenotype/cell stem origin

Germinal centre B-cells, the translocations appears at the pre B-stage of the B-cell differentiation.

Epidemiology

t(2;18)(p11;q21) is found in 8 cases (0.5% of all cases with abnormal karyotype) (Konishi H et al., 1990; Leroux D et al., 1990; Bertheas M-F et al., 1991; Juneja S et al., 1997; Horsman DE et al., 2001; Henderson L-J et al., 2004; Bentley G et al., 2005; Babu Rao V et al., 2006). The sex ratio is balanced M:F=1:1. The anomaly is observed mostly in older patients (average age 56 years; range 47-72).

Cytogenetics

t(2;18) as a sole anomaly is found only in one case. The other cases are with additional anomalies: 5 cases are with 1 to 4 anomalies and 3 cases are with highly complex karyotypes. In three cases the stemline with t(2;18) is evaluated to subclones with secondary chromosome aberrations.

Additional anomalies Most of the additional anomalies frequently associated with t(14;18) and FL are also present in the described cases with t(2;18): +12 (1 case), +7 (3 cases), 6q- (1 case), +X (3 cases; one with additional deleted X in q22), +5 (1 case), +8 (2 cases) and +der(18)t(2;18) (3 cases; one with 2 copies). In one case t(8;14)(q24;q32) is observed and in another two copies of its minor variant t(8;22)(q24q11) are present. Additional abnormalities of the following chromosomes are also described: chromosome 1 (3 cases - all of them are with 1p or 1q gains as a result of duplication of the segment 1q21q42 (one case) and unbalanced translocations of the segments 1p11qter, 1q11qter and 1q21qter to the different recipient chromosomes including 1, 3, 9, 13 and 15), chromosome 3 (3 cases - two with -3, +3 and unbalanced translocations involving 3p11, q12 and q21 and one with t(3;3)(p21;q23) as a second anomaly in the stemline), chromosome 13 (2 cases - one with interstitial deletion of the segment q13q31 and one with translocation involving 13q34) and chromosome 15 (3 cases - one with interstitial deletion of the segment 15q12q15 and translocations involving 15q12, one with der(15)t(1;15)(p11;p11) and one with t(6;15)). Gains of 2p, 18 and 21 as well as losses of 1p, 10q and 17p that are frequently associated with FL with t(14;18) are not reported.

Disease

Other B-lymphoproliferative disorders

Epidemiology

(2;18) is found in 5 cases: 2 cases (0.14% of all cases with abnormal karyotype) with diffuse large B-cell lymphoma (DLBCL) (females; one with age 56 year)(Hillion J et al., 1991; Macpherson N et al., 1999), 1 case (0.14% of all cases with abnormal karyotype) with mature B-cell neoplasm, NOS (MBCN) (male) (Tomita N et al,. 2009), 1 case (0.11% of all cases with abnormal karyotype) with Burkitt lymphoma/leukemia (BL) (37-year-old female) (Hillion J et al.,1991) and 1 case (0.04% of all cases with abnormal karyotype) with chronic lymphocytic leukemia (CLL) (55-year-old male) (Dyer MJS et al., 1994).

Cytogenetics

Only the case with CLL is with one additional anomaly. All remaining cases are with complex karyotypes.

Additional anomalies Some of the additional anomalies associated with t(14;18) are found: +12 (1 case with CLL and 1 with DLBCL), +X (1 case with DLBCL) and +18 (1 case with DLBCL). Abnormalities of chromosome 1 are reported in all cases except in the patient with CLL (1 case is with +der(1)(q12), 1 with t(1;9)(p34;p22), 1 with i(1)(q10) and 1 with add(1)(p36)). Chromosome 3 abnormalities is present in 2 cases with DLBCL - one is with add(3)(p25) and add(3)(q21) and one with t(3;22)(q27;q11). In one case with DLBCL t(8;14)(q24;q32) is described and in another with MBCN the same anomaly in combination with der(14)t(8;14)(q24;q32).

Genes involved and proteins

IGK (Immunoglobulin Kappa)

Location 2p11.2

DNA/RNA IGK contains approximately 40 functional IgV (variable) genes, 5 IgKJ (Joining) genes and one IgKC (Constant) gene.

Protein

IGK encodes the immunoglobulin light chain kappa. The kappa chain is composed of an N-terminal variable region containing the antigen-binding site (encoded by one of the V and one of the J genes) and a C-terminal constant region (encoded by the C region gene). This structure of the Ig K chain is assembled by V-J rearrangement events followed by joining of the C gene to the V-J segment by RNA splicing.

BCL2 (B-Cell Leukemia/Lymphoma 2)

Location 18q21.3

DNA/RNA BCL2 contains 3 exons and produces by alternative splicing 3 types of transcripts (a, b and c) encoding 2 different protein isoforms.

Protein

BCL2 belongs to the Bcl2 antiapoptotic Bcl2 family proteins (BCL2L2 (BCLW), MCL1, BCL2A1 (BFL1)) that have similar 3D structure and four Bcl2 homology (BH1-4) domains. Bcl2 blocks cell death preventing the release of cytochrome c from the mitochondria by inactivating their proapoptotic Bcl2 family counterparts (BAX, BAK1, BCL2L11 (BIM), BID, BAD, BIK, BMF) and by inhibition the inositol 1,4,5-triphosphate receptor (Rong YP et al., 2009; Monaco G et al., 2012).

KDSR (3-ketodihydrosphingosine reductase)

Location 18q21.3

DNA/RNA KDSR contains 10 exons and its transcription produces 13 different mRNAs, 11 alternatively spliced variants and 2 unspliced forms.

Protein

KDSR encodes a putative secreted protein of 36kD that is a member of the short-chain dehydrogenases/reductases family. The protein localizes to the endoplasmic reticulum (ER) and catalyzes the reduction of 3-ketodihyrosphingosine to dihydrosphingosine in the "de novo" synthetic pathway of ceramide. Contains an N-terminal

transmembrane segment, followed by a large hydrophilic domain, 2 C-terminal transmembrane segments, and a KKxx-type endoplasmic reticulum (ER) retention signal at its C terminus.

Result of the chromosomal anomaly

Hybrid gene

No hybrid gene is created. T(2;18) IgK/BCL2 leads to the juxtaposition of BCL2 near the enhancer sequences of the IgK gene. In contrast to the distribution of the breakpoints in BCL2 of the classical t(14;18) that are clustered in the majority of cases within the major (MBR) and minor breakpoint cluster region and more rarely within the 5'- flanking region of BCL2, the breakpoints in the BCL2 locus in t(2;18) occurs only in the 5' flanking region of the BCL gene termed the variant cluster region (VCR) (Larsen CJ et al., 1990; Hillion J et al., 1991; Bertheas M-F et al., 1992; Yabumoto K et al., 1996). The BCL2 coding region is not affected, because the breakpoints in VCR are distributed upstream of the translational initiation site of the BCL2 gene. On the other hand the locations of the breakpoints in the IgK gene are diverse. DNA breakage as a result of 5'-BCL2/IgK junctions have been described in the region of the intronic sequences, joining segments and k-deleting element (Yonetani N et al., 2001). In some cases with t(2;18) head-to-tail configuration of the BCL2 and IgK genes have been recognized. In the molecular variant IgK/KDSR (FVT-1) the breakpoints on 18q21 and 2p11 occurred in the last intron of FVT-1 and within the J4 segment of the Jk region respectively. As a result of the translocation the promoting region and the 5' part of the coding sequence of FVT-1 is juxtaposed to the V_k -J_k region of the kappa light chain on the der(2) chromosome.

Fusion protein

Fusion protein in the cases with BCL2/IgK rearrangements is not produced. The kappa immunoglobulin enhancer induces BCL2 overexpression.

Oncogenesis

The consequence of t(2;18) is the same as in the t(14;18). The overproduction of the Bcl2 protein blocks the apoptosis and promotes prolonged B-cell survival. But the differences in the molecular structure of both rearrangements possibly predispose difference in the levels of BCL2 expression. It was found that the cases and tumor cell lines with 5'-BCL2/Ig (including 5'-BCL2/IgK) rearrangements have markedly higher levels of BCL transcripts (as well as expression of BCL2 protein by immunocytochemistry staining) than those of BCL2/IgH with breakpoints in MBR or 3'-MBR (Dyer MJS et al., 1993; Yonetani N et al., 2001). In the molecular variant IgK/FVT-1 the FVT-1 disruption resulted in the constitution of a chimeric V_k -J_k-5' FVT-1 gene in a tail-to-tail configuration. On the other hand the BCL2 is juxtaposed to the kappa light chain locus in the vicinity of the 5' kappa gene enhancer leading to its overexpression. Therefore the molecular pathogenesis of this variant of t(2;18) is also linked to the deregulation of BCL2 and not to the FVT-1.

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