

Leukaemia Section

Short Communication

del(18)(p11)

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Abstract

Review on del(18)(p11) in haematological malignancies, with data on the genes possibly involved.

Keywords

Chromosome 18; Chronic myeloid leukemia; Myelodysplastic syndromes; Acute myeloid leukemia; Acute lymphoblastic leukemia; Follicular lymphoma

Clinics and pathology

del(18)(p11) is a very rare structural anomaly found only in 24 cases with onco-hematological disorders. This deletion has been observed in both myeloid (14 cases) and lymphoid (10 cases) malignancies and has been predominantly associated with a complex karyotype. In all cases 18p- is presented as a single copy in the karyotype. The anomaly was determined by conventional cytogenetic as terminal deletion with sub-band location of the breakpoint in 18p11.2. Microarray comparative genome hybridization (aCGH) studies in patients with acute myeloid leukemia have demonstrated that the deleted segment in 18p could be also interstitial and variable in size as has been proven in other tumor associated deletions. Three submicroscopic deleted regions have been identified - 18p11.32-p11.31, 18p11.23 and 18p11.22-p11.21 (Itzhar et al, 2011).

Disease

Acute Myeloid Leukemia (AML)

Epidemiology

del(18)(p11) is found in 9 cases (0.1% of all AML cases with an abnormal karyotype) (Alimena et al.,

1981; Brodeur et al., 1983; GFCH, 1990; Lawler et al., 1990; Mohamed et al., 1993; Davey et al., 1995; Krauter et al., 1998; Babicka et al., 2007; Kasyan et al., 2010) - 1 case with M1 French-American-British (FAB) phenotype, 2 cases with M2, 1 case with M3, 1 case with M4, 1 case with M6 and 3 with AML, NOS (one diagnosed as therapy related AML).

The sex ratio is significantly unbalanced, near M:F=3.5:1.

The age is documented in 5 cases: 6 and 35 (M2), 59 (M3), 42 (M4) and 61 (M6).

Cytogenetics

In 5 cases del(18)(p11) is found in complex karyotypes and in one as a sole anomaly. Three cases are with -5/del(5q), two with +8 and one case of each of the following well known rearrangements: -7; del(17p); t(8;21)(q22;q22); t(17;20)(q21;q11) in a M3 (RARA not checked). In one case both arms of chromosome 18 are affected - der(18)del(18)(p11)del(18)(q21). In 3 cases 18p- is associated with sex chromosome abnormalities - 2 with a loss of Y chromosome and one with del(X)(q26).

Disease

Other Myeloproliferative Disorders

Epidemiology

del(18)(p11) is described in 2 cases (one male and one female) with chronic myeloid leukemia (CML) (Ohyashiki et al., 1997; Sun et al., 2011), 2 cases (males) with a myelodysplastic syndrome (Cerretini et al., 2002; Volkert et al., 2014) and one case (female) with primary myelofibrosis (PMF) involving a lymph node (Hu et al., 2009).

Cytogenetics

In 2 cases with MDS and one case with CML del(18)(p11) is associated with a complex karyotype, in one case with CML it is a second event and in one case (with PMF) it is a sole anomaly.

In the two cases with CML 18p- anomaly is present in additional deviating sub-clones (sidelines) and in one case with MDS in two clones with dic(17;20)(p11-12;q11) and dic(18;18)(p11;p11).

Disease

Acute Lymphoblastic Leukemia (ALL)

Epidemiology

del(18)(p11) is found in 8 cases with ALL (0.08% of all ALL cases with an abnormal karyotype) (Oshimura et al., 1977; Kanerva et al., 2002; van der Burg et al., 2002; Soulier et al., 2003; Karst et al., 2006; Shin et al., 2011; Schmiegelow et al., 2012; Lundin et al., 2014).

The sex ratio is significantly unbalanced, near M:F=1.7:1.

The anomaly has been observed in young, as well as older patients (average age 22.6 years; range 5-65).

Cytogenetics

In 5 cases del(18)(p11) is found in complex karyotypes and in 3 cases it is accompanied with second anomalies - der(21) in two cases and dup(18q)(q11q11) in one (unrelated clone). In 4 of the 5 cases with complex karyotypes 18p- is associated with one or more deletions including 6p-, 9p-, 11q- and 12p- and in two cases with t(7;14)(p13;q32) and t(14;18)(q32;q21) (Shin et al., 2011), respectively.

Disease

Follicular lymphoma (FL)

Cytogenetics

del(18)(p11) is reported in 2 cases with FL (Bosga-Bouwer et al., 2003; Horsman et al., 2003). Both have hyperdiploid, highly complex karyotypes.

Genetics

A tumor suppressor gene(s) (TSG) important to the described hematological malignances may be involved in the molecular pathogenesis of del(18)(p11).

A number of TSG candidates are mapped in the deleted segment 18p11.2->18pter including PTPN2 (18p11.21), LDLRAD4 (C18orf1) (18p11.21), RALBP1 (18p11.22), PPP4R1 (18p11.22), PTPRM (18p11.23), EPB41L3 (18p11.31), L3MBTL4 (18p11.31), TGIF1 (18p11.31), ZEP161 (18p11.31) and SMCHD1 (18p11.32).

Almost all are implicated in the pathogenesis of a variety of solid tumors, but there are several lines of data suggesting that four of them (PTPN2, PTPRM, TGIF1 and SMCHD1) could also have a role in leukogenesis and respectively may act as TSG in the hematopoietic system.

Genes involved and proteins

PTPN2 (protein tyrosine phosphatase, non-receptor type 2)

Location

18p11.21

Protein

PTPN2 (Tyrosine-protein phosphatase non-receptor type2) is a negative regulator of multiple signaling pathways, including IL2 (interleukin 2) mediated JAK2/STAT cascade and is inactivated by nonsense mutation in 5% and deleted in 6% of the cases with adult acute T-cell lymphoblastic leukemia (Kleppe et al., 2010).

PTPRM (protein tyrosine phosphatase, receptor type M)

Location

18p11.23

Protein

PTPRM (Tyrosine-protein phosphatase, receptor type M) is targeted by aCGH within the deleted region 18p11.23 found in 17 cases with AML.

The protein encoded by this gene is involved in cell-cell adhesion through hemophilic interactions. Hypermethylation of PTPRM in cases with ALL (Stevenson et al, 2013) and submicroscopic deletion of PTPRM in cases of adult T cell leukemia/lymphoma have been observed (Kataoka et al 2015).

TGIF1 (TGFB induced factor homeobox 1)

Location

18p11.31

Protein

TGIF1 (TG-interacting factor 1) is targeted by aCGH within the deleted region 18p11.32p11.31 found in 14 cases with AML.

The protein encoded by this gene plays an essential role in the regulation of hematopoiesis inhibiting the signaling pathways of RA (retinoic acid) and TGFB1 (transforming growth factor beta) by transcriptional repression of SMAD2.

It has been demonstrated that TGIF1 is a negative regulator of KMT2A (MLL)-rearranged AML (Willer et al, 2014).

SMCHD1 (structural maintenance of chromosomes flexible hinge domain containing 1)

Location

18p11.32

Protein

SMCHD1 (Structural maintenance of chromosome flexible hinge domain containing 1) is also targeted by aCGH within the region 18p11.32p11.31.

This gene encodes a protein required for the maintenance of an X chromosome inactivation in females. It has been reported that SMCHD1 is associated with increased tumorigenesis in a mouse model.

Global gene expressing profiling revealed that SMCHD1 normally repress genes activated by MLL- chimeric fusion proteins in leukemia (Leong et al, 2012).

These data have suggested that the loss of SMCHD1 may cause hematological malignances of both cell lineage - myeloid and lymphoid.

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