12p rearrangements in CLL

Clinics and Pathology

Disease Chronic lymphoproliferative leukemia (CLL)

Epidemiology A 12p rearrangement is observed in about 1.4% CLL cases usually as part of a complex karyotype with multiple abnormalities, but about 7.7% of these are apparently sole cytogenetic abnormality.

Prognosis 12p rearrangements in CLL probably are early chromosome defects that are not associated with the classical DNA gains and losses known to be present in the majority of CLL. An atypical morphology and immunophenotype may be present in cases with 12p rearrangements; and frequently there is disease progression. Transformation of CLL to PLL has been observed in cases with a 12p abnormality.

Cytogenetics

Cytogenetics Morphological Aberrations of 12p in CLL are often subtle addition to 12p (n=15), followed by translocation (n=12), deletion (n=10), derivative (n=8), dicentric (n=3), inversion (n=2), and isochromosome (n=1). The breakpoint is commonly 12p13 in 31 cases (especially, in almost all del 12p cases), 12p12 in 7 cases, 12p11 in 10 cases, and 12p10 in 1 case.

The recurring 12p rearrangements in CLL are: 5 translocations involving chromosomes 12 and 13, making it the most common recurring 12p translocation. In two of the five cases translocation, t(12;13) is the sole cytogenetic abnormality, but the breakpoints are different, t(12;13)(p13;q22) and t(12;13)(p11;q14). Translocation, t(12;13) has also been found in patients with chronic myelogenous leukemia (CML) in transformation, myelodysplastic syndrome (MDS), acute non lymphocytic leukemia (ANLL), B and T- acute lymphocytic leukemias (ALL). The t(12;13) is heterogeneous at the molecular level. A single case of ANLL has been reported with an ETV6-CDX2 fusion and ectopic expression of normal CDX2 but two other t(12;13) positive ANLL patients did not have CDX2 involvement. FISH analysis has suggested that the chromosome 13 breakpoints are different in myeloid and lymphoid disease. ETV6 seems to be involved in some cases but not others.

The other recurring translocation in CLL involved chromosomes 12 and 17 in 3 cases, 1 a translocation and 2 are derivative 12 resulting from a translocation between 12 and 17 chromosomes. This translocation is observed in patients with acute leukemia at diagnosis or relapse and who had a poor prognosis .

Though, t(12;22)(p13;q11) is a consistent myeloid change there are at least 3 CLL cases with this translocation and one with ETV6 gene deletion. One case of CLL had a t(9;12)(q34;p11) as the sole abnormality, the breakpoint on chromosome 9 coincided with that observed in 6 other cases with acute lymphoblastic leukemia (ALL), acute non lymphocytic leukemia (ANLL) and chronic myeloid leukemia

(CML) while the 12 breakpoint 12p13 was different. Two different fusion breakpoints are described; ETV6 exon 4 fused in frame to ABL exon 2 (Type A) and ETV6 exon 5 fused in frame to ABL exon 2 (Type B); ETV6 maintains the HLH domain and ABL the tyrosine kinase domain. Characterization of the 12p breakpoint of 12p rearrangements in lymphoid and myeloid malignancy in context to ETV expression may throw light on the lineage specificity of these rearrangements and their role in the malignancy.

Other translocations of 12p observed in single CLL cases are der(12) t(12;18)(p13;q24), der(12) t(12;12)(p13;q13), der(12)t(1;12)(q11;p12), der(12)t(10;12) (q11;p13), der(12)t(7;12)(p13;p13), der(12)t(12;15)(p12;q13-15), t(5;12;19)(q15;p11;q13), t(6;12)(p21;p13), t(6;10;12)(q15;q22;p13), t(12;14)(p13;q21), dic(9;12)(p24;p13), dic(12;15)(p13;p11) and dic(3;12)(p21;p13)
The inv(12) in 3 cases, is supernumerary in two cases +inv(12)(p13q24) and inv(12)(p13q13)x2, and ?inv(12)(p11q23) in one case.

Summary of 12p rea in CLL

Breakpoint : -

46,XY,?t(4;11)(q?;q?),del(6)(q21q23),del(11)(q?),?del(12)(p?)
45,XY,del(7)(q31),-11,add(12)(p?)/46,idem,+6,del(6)(q?)x2/44,XY,der(3;4)(p10;q10)
46,XY,add(12)(p?),del(13)(q?),del(17)(q?)

Breakpoint : 12p10

47,XX,i(12)(p10),+i(12)(q10),del(14)(q24)

Breakpoint : 12p11

48,XY,+3,+del(5)(q15),t(5;12;19)(q15;p11;q13),del(7)(q11)
44,XX,-3,add(12)(p11),der(17;18)(q10;q10)/44,idem,der(17)t(3;17)(p11;p13)ins(17;?)(p13;?)/45,XY,add(3)(p11),der(17;18)
43-46,X,-Y,del(2)(p23),del(6)(q21),del(7)(q32),del(11)(q21),-12,+t(12;17)(p11;q11),t(14;14)(q11;q32),-17,-18
47,XY,+12,t(12;13)(p11;q14)
46,XX,t(12;13)(p11;q14)
46,XY,t(2;8)(p11;q24),t(14;18)(q32;q21)/47,idem,-t(2;8),add(12)(p11),-13,der(17)t(13;17)(q14-21;q23-25),del(19)(p13),+2mar
46,XX,+del(7)(q22),t(11;11)(p13;p15),del(12)(p11),add(13)(p13),-18
46,XY,t(9;12)(q34;p11)
46,XY,t(3;4)(q28;q31),del(11)(q14q24)/92,idemx2/46,idem,del(13)(q12q14)/46,XY,del(6)(?q21q24),del(11)(q22q25),del(13),t(13;16)(q?21;p11)/46,XY,del(6),t(13;16),der(17)t(17;18)(p11;q11)/46,XY,inv(3)(p14q?27),del(4)(q31),del(11)(q14q24),?inv(12)(p11q23)

Breakpoint : 12p12

45,XX,dic(2;17)(q37;p11),der(12)t(12;17)(p12;q11),del(13)(q14q31)/45,idem,add(19)(p1?3)
46,XX,-7,der(12)t(12;17)(p12;q11),der(15)t(7;15)(q11;q26),der(17)del(17)(p11)t(12;17)(?;p11),add(18)(p11)/47,idem,+12,-add(18)/45,idem,der(3)t(3;15)(p21;q15),+7,der(8)t(8;22)(p11;q11),-15,-der(15),-add(18),-22/46,XX,+12,add(17)(p11),-20,-21,+mar
46,XX,t(12;13)(p12;q14),inc
46,XY,+der(12)t(12;15)(p12;q13-15),der(14;17)(q10;q10)/46,idem,add(1)(q21)
??,XY,del(1)(q?),t(1;10)(q11;p1?5),der(12)t(1;12)(q11;p12)

43,X,add(X)(q28),-1,+2,-7,-9,add(9)(q34),del(10)(q24),-11,add(12)(p12),-21, +mar
46,XY,del(4)(q21q33),del(6)(q23q25),add(12)(p12)

Breakpoint : 12p13

44,XX,-6,dic(9;12)(p24;p13),der(17)t(6;17)(q15;p13)
43,XY,t(1;14)(p32;q32),-4,t(6;12)(q21;p13),add(7)(p22),-9,-11,add(13)(q34),add(17)(p13)
45,XX,ins(1;?)(q11;?),del(6)(q23),add(7)(q36),add(12)(p13),t(13;15)(q?;q?),add(14)(q32)
46,XY,del(6)(q15q25)/45,idem,der(12;17)t(12;17)(q15;p11)t(12;18)(p13;q24),der(18)t(12;18)(q21;q23)
44,XX,add(9)(q34),add(11)(p15),dic(12;15)(p13;p11),dic(17;18)(p11;p11)
47,XX,add(12)(p13),+der(12)t(12;22)(p13;q11),del(22)(q11)/47,idem,del(9) (p21) Tel deletion
47,XY,+add(12)(p12)
46,XY,add(12)(p13)
47-48,XX,add(12)(p13),+2mar
46,XX,-3,dic(3;12)(p21;p13),der(6)add(6)(p25)del(6)(q16q22),i(8)(q10),del(11)(q14q24)
44,XY,-3,der(8;17)(q10;q10),add(12)(p13),der(12;?)dic(12;?)(p1?1;?)hsr(?), -15,add(15)(p11),+mar
46,XX,del(11)(q13q23),del(12)(p?13),add(17)(q25)
47,XY,+inv(12)(p13q24)
46,XY,del(6)(q23q27),t(12;14)(p13;q21)/46,idem,del(7)(q32q36)/46,XY,t(1;9)(p36;q22)/46,XY,del(6)(q15q26)/46,XY,del(17)(p11)/46,XY,t(6;12)(p22;q13)/46,XY,add(7)(q35)
44-45,XY,add(1)(q23),del(1)(q21),-8,-11,+add(12)(p13),-13,der(14)t(11;14)(q23;q32),-21,+2mar
47,XX,+12,t(12;22)(p13;q11),t(14;19)
82,XXY,-Y,-6,-6,-7,-8,-8,-9,-10,t(11;14)(q13;q32),add(12)(p13)x2,t(13;14)(q11;q32),-14,-17,-18,-19,-20,-22,+4mar
44-46,XY,del(1)(q42),t(2;13)(p21-23;q14),dup(3)(?q27q29),del(6)(p23p25),-9, -11,t(11;14),der(12)qdp(12)(q13q15)trp(12)(q21q22)t(12;12)(p13;q13),-15,-17, +5mar
46,XY,der(1)del(1)(p11p21)del(1)(q22q25),del(2)(q31),del(6)(q13-15),t(11;14)(q13;q32),+12,inv(12)(p13q13)x2
46,XX,add(3)(q21)/46,idem,del(12)(p13),t(?13;14)(q22;q32),del(18)(q21)
46,XX,del(1)(q32),add(11)(p14-15),del(12)(p13)
46,XX,del(1)(q21)/46,XX,t(?13;14)(q22;q32)/46,XX,del(12)(p13),t(?13;14),add(17)(q25)
46,XX,-9,+del(12)(p13),t(?13;14)(q22;q32)/46,XX,del(1)(q32),del(3)(p25),-9,+del(12),t(?13;14),add(16)(p13)
46,XY,del(12)(p13),add(17)(p13)
47,XY,add(1)(p?),del(3)(p2?),add(11)(p14),+13/47,idem,del(11)(q21),del(12)(p13),del(13)(q22),add(14)(q32)
46,XX,r(4)(p16q31),t(4;6)(q31;q26),-10,t(10;12)(q24;q22),add(12)(p13),del(14)(q21),+mar
48,XY,+der(3)del(3)(p?25)del(3)(q?21),t(11;14)(q13;q32),+der(12)t(10;12)(q11;p13)
46,XY,del(12)(p13)
46,XY,add(1)(p36),del(6)(q15),t(6;10;12)(q15;q22;p13),t(11;14)(q13;q32),del(12)(p?),+der(12)t(7;12)(p13;p13)

TOTAL :

12p13=31, 12p12=7, 12p11=10, 12p10=1
add=15, der=8, del =10, t=12, inv=2, i=1, dic=3

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