Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Leukaemia Section
Short Communication

del(13q) in chronic lymphocytic leukemia

Luis Miguel Juárez Salcedo, Samir Dalia

Principe de Asturias University Hospital, Madrid, Spain. Dr.luisjuarez@gmail.com (LMJ); Oncology and Hematology, Mercy Clinic Joplin, Joplin, MO, USA sdalia@gmail.com (SD)

Published in Atlas Database: October 2016
Online updated version : http://AtlasGeneticsOncology.org/Anomalies/del13qCLLID1208.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/68529/10-2016-del13qCLLID1208.pdf
DOI: 10.4267/2042/68529

Abstract

Review on del(13q) in chronic lymphocytic leukemia, with data on clinics, and the genes involved.

Keywords
Chronic Lymphocytic Leukemia; chromosome 1; del(13q)

Clinics and pathology

Disease

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults, with a highly variable clinical course, ranging from very indolent cases to a very aggressive and rapidly progressing disease (Puiggros et al., 2014). Although is characterized by a relatively stable genome, acquired genetic aberrations have an important role in CLL prognosis. The most frequent chromosomal abnormalities are partial losses of one affected chromosome (del(6q), del(11q), del(13q) or del(17p)) and gains of entire chromosomes (trisomy 12). (Baliakas et al., 2014).

Etiology

The pathogenic role of del(13q) in CLL has been related to lack of B-cell proliferation control allegedly determined by deletion of the DLEU2/ MIR15A/ MIR16-1 locus, which is known to contain negative regulators of the expression of the BCL2 gene (Cimmino et al., 2005; Klein et al., 2010).
The RB1 gene is involved in the regulation of cell cycle progression and genomic stability.
Biallelic 13q deletions are characteristically small and do not involve RB1 deletions, nevertheless their clinical impact has been controversial. Thus, the potential effect could be masked by the size of the deleted region or the inactivation of the remaining allele by other mechanism.
Related to the size of abnormal clone (detected by FISH), patients with a higher percentage of altered nuclei (cut-off point ranged from 65-90%) have a bad prognosis (van Dyke et al., 2010).
Those patients with large 13q losses showed downregulation of ten genes including TPT1 (TCTP), which in involved in prosurvival and growth signaling through inhibition of BAX-induced apoptosis and overexpression of 53 genes.
Other genetic abnormalities: GPS2 (AMF), GPI, BSG, LGALS1, PAK2, PARVBand VIM participate in cell motility, adhesion, and regulation of cell proliferation, tumor cell migration, metastasis, angiogenesis and apoptosis (Rodriguez et al., 2012).

Epidemiology

Del(13q) involving the band q14, found in more than 50% of CLL patients, is the most common cytogenetic abnormality detected by FISH, and has been associated with good prognosis.
Del(13q) as the sole aberration occurs in the hemizygous state in approximately 75-80% of cases and in the homozygous state in the remaining 20-25% (Migliazza et al., 2001).

Cytology

The CLL-cells characteristics are the same, independently of the chromosomal abnormalities. The peripheral blood smear of patients with CLL demonstrates a lymphocytosis. The leukemic cells are typically small, mature appearing lymphocytes with a dense nucleus, partially aggregated (clumped) chromatin, and without discernible nucleoli. There is

a narrow border of clear to slightly basophilic cytoplasm.

Cytogenetics

Two anatomical landmarks have been proposed for the characterization of 13q deletion in CLL:

I- The minimal deleted region (MDR), which comprised the DLEU2 gene, the MIR15A/MIR16-1 cluster, and the first exon of the DLEU1 gene. (Liu et al., 1997; Lagos-Quintana et al., 2002)

II-The RB1 gene, localized at chromosomal band 13q14.1-q14.2 that can be considered, when found deleted, as the marker of 13q deletion with larger chromosome losses (Ouillette et al., 2008; Parker et al., 2011).

Other genes located in 13q, such as DLEU7 or TRIM13 could cooperate in the tumoral suppressor activity.

Treatment

Del(13q) patients, responds better to alkylating agents (fludarabine and chorambucil) and potentially can have a long term PFS with these therapies unlike del(17p) patients.

Prognosis

Del(13q) in any form has a better prognosis than del(17p) (3-8% of CLL at diagnosis and up 30% in refractory CLL cases) or del(11q) (detected in 5-20% of CLL patients) (Döhner et al., 2000).

It has been extensively demonstrated that large 13q losses involving RB1 gene are related to shorter time to first treatment (TTFT) and overall survival (OS) than those small deletions encompassing only MIR15A/MIR16-1.

Although CLL with 13q deletion as the sole cytogenetic abnormality usually have good prognosis, more aggressive clinical courses are documented for del(13q)-only CLL carrying higher percentage of 13q-deleted nuclei. Many published studies had demonstrated the prognosis heterogeneity that occurs in patients with this chromosomal abnormality, which can be revealed by FISH analysis of both deletion load and deletion size, suggesting the existence of additional factors (deletions of different sizes) in defining del(13q)-only CLL prognosis (Dal Bo et al., 2011).

References

Baliakas P, Hadzidimitriou A, Sutton LA, et al. Recurrent mutations refine prognosis in chronic lymphocytic leukemia Leukemia 2015 Feb;29(2):329-36

Cimmino A, Calin GA, Fabbri M, Iorio MV, Ferracin M, Shimizu M, Wojcik SE, Aqeilan RI, Zupo S, Dono M, Rassenti L, Alder H, Volinia S, Liu CG, Kipps TJ, Negrini M, Croce CM. miR-15 and miR-16 induce apoptosis by targeting BCL2 Proc Natl Acad Sci U S A 2005 Sep 27;102(39):13944-9

Dal Bo M, Rossi FM, Rossi D, Deambrogi C, Bertoni F, Del Giudice I, Palumbo G, Nanni M, Rinaldi A, Kwee I, Tissino E, Corradini G, Gozzetti A, Cencini E, Ladetto M, Coletta AM, Luciano F, Bulian P, Pozzato G, Laurenti L, Forconi F, Di Raimondo F, Marasca R, Del Poeta G, Gaidano G, Foà R, Guarini A, Gattei V. 13q14 deletion size and number of deleted cells both influence prognosis in chronic lymphocytic leukemia Genes Chromosomes Cancer 2011 Aug;50(8):633-43

Klein U, Lia M, Crespo M, Siegel R, Shen Q, Mo T, Ambesi-Impiombato A, Califano A, Migliazza A, Bhagat G, Dalla-Favera R. The DLEU2/miR-15a/16-1 cluster controls B cell proliferation and its deletion leads to chronic lymphocytic leukemia Cancer Cell 2010 Jan 19;17(1):28-40

Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs Science 2001 Oct 26;294(5543):853-8

Liu Y, Corcoran M, Rasool O, et al. Cloning of two candidate tumor suppressor genes within a 10 kb region on chromosome 13q14, frequently deleted in chronic lymphocytic leukemia Oncogene 1997 Nov 13;15(20):2463-73

Migliazza A, Bosch F, Komatsu H, Cayanis E, Martinotti S, Toniato E, Guccione E, Qu X, Chien M, Murty VV, Gaidano G, Inghirami G, Zhang P, Fischer S, Kalachikov SM, Russo J, Edelman I, Efstratiadis A, Dalla-Favera R. Nucleotide sequence, transcription map, and mutation analysis of the 13q14 chromosomal region deleted in B-cell chronic lymphocytic leukemia Blood 2001 Apr 1;97(7):2098-104

Ouillette P, Erba H, Kujawski L, Kaminski M, Shedden K, Malek SN. Integrated genomic profiling of chronic lymphocytic leukemia identifies subtypes of deletion 13q14 Cancer Res 2008 Feb 15;68(4):1012-21

Parker H, Rose-Zerilli MJ, Parker A, Chaplin T, Wade R, Gardiner A, Griffiths M, Collins A, Young BD, Oscier DG, Strefford JC. 13q deletion anatomy and disease progression in patients with chronic lymphocytic leukemia Leukemia 2011 Mar;25(3):489-97

Puiggros A, Blanco G, Espinet B. Genetic abnormalities in chronic lymphocytic leukemia: where we are and where we go Biomed Res Int 2014;2014:435983

Rodríguez AE, Hernández J, Benito R, Gutiérrez NC, García JL, Hernández-Sánchez M, Risueño A, Sarasquete ME, Fermin E, Fisac R, de Coca AG, Martín-Núñez G, de Las Heras N, Recio I, Gutiérrez O, De Las Rivas J, González M, Hernández-Rivas JM. Molecular characterization of chronic lymphocytic leukemia patients with a high number of losses in 13q14 PLoS One 2012;7(11):e48485

Van Dyke DL, Shanafelt TD, Call TG, Zent CS, Smoley SA, Rabe KG, Schwager SM, Sonbert JC, Slager SL, Kay NE. A comprehensive evaluation of the prognostic significance of 13q deletions in patients with B-chronic lymphocytic leukaemia Br J Haematol 2010 Feb;148(4):544-50

This article should be referenced as such:

Juárez Salcedo LM, Dalia S. del(13q) in chronic lymphocytic leukemia. Atlas Genet Cytogenet Oncol Haematol. 2017; 21(8):292-293.