Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Leukaemia Section

Review

Acute lymphoblastic leukemia in Down syndrome

Karen M. Chisholm

Department of Laboratories, Seattle Children's Hospital, Seattle, WA, USA;
karen.chisholm@seattlechildrens.org

Published in Atlas Database: June 2017
Online updated version : http://AtlasGeneticsOncology.org/Anomalies/LymphoidLeukDownSyndromeID1784.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/68933/06-2017-LymphoidLeukDownSyndromeID1784.pdf
DOI: 10.4267/2042/68933

Abstract

Review on acute lymphoblastic leukemia in Down syndrome, with data on clinics, pathology, and involved genes.

KEYWORDS
Down syndrome; leukemia; lymphoblastic leukemia.

Clinics and pathology

Disease

Acute lymphoblastic leukemia (ALL) associated with Down syndrome (ALL-DS), is predominantly a B lymphoblastic leukemia, with only very rare cases of mature B cell ALL (Burkitt leukemia) and T-cell ALL.

Epidemiology

Trisomy 21 has an incidence of approximately 1 in 700 live births. The frequency of acute lymphoblastic leukemia in Down syndrome (ALL-DS) is estimated at 1 in 300 (Lange, 2000). The incidence of ALL-DS <5 years of age is 40.7 times greater than that in individuals without Down syndrome of the same age; in addition, there remains an increased risk of ALL-DS compared to those without Down syndrome up to the age of 30 years (Hasle et al., 2000). However, unlike those without Down syndrome, ALL -DS usually does not present in patients <1 year of age.

Clinics

Other than the lack of presentation in children <1 year of age, ALL-DS has similar clinical features to ALL in children without Down syndrome, including age, sex, presenting white blood cell count, and NCI risk group (Maloney et al., 2010). Some studies identify similar rates of mediastinal masses and central nervous system involvement at diagnosis in those with ALL-DS and those with ALL without Down syndrome, but other studies identified decreased CNS disease and mediastinal masses in those with ALL-DS (Maloney, 2011).

Cytology

Blasts are characterized as small to medium in size with high nuclear-to-cytoplasmic ratios, round to irregular nuclei, smooth chromatin, and scant deeply basophilic agranular cytoplasm.

Pathology

The blasts of ALL-DS usually have an immature B cell phenotype, expressing CD19, CD10, and CD79a.

Cytogenetics

The cytogenetics of ALL-DS differs from the cytogenetics in those with ALL not associated with Down syndrome. The children with ALL-DS have a

decreased frequency of favorable cytogenetics including high hyperdiploidy, trisomies of chromosomes 4, 10, and 17, and the t(12;21) translocation compared to children without Down syndrome (Maloney et al., 2010; Bruwier and Chantrain, 2012); these ALL-DS children also have a decreased frequency of unfavorable translocations such as t(9;22) and 11q23 (MLL) rearrangements. Approximately 50-60% of ALL-DS have been found to have CRLF2 gene rearrangements by FISH or RT-PCR (Mullighan et al., 2009; Hertzberg et al., 2010). The most common rearrangement is a deletion in the pseudoautosomal region 1 (PAR1) of Xp22.33/Yp11 resulting in a fusion between the first noncoding exon on P2RY8 with the entire coding region of CRLF2 (del(X)(p22.33p22.33)/del(Y)(p11p11)) (Mullighan et al., 2009). Less commonly, CRLF2 rearrangements with IGH (immunoglobulin heavy chain locus) are identified (t(X;14)(p22;q32)/t(Y;14)(p11;q32)). These fusions result in overexpression of CRLF2. Overexpression of CRFL2 has not been found to be correlated with outcome.

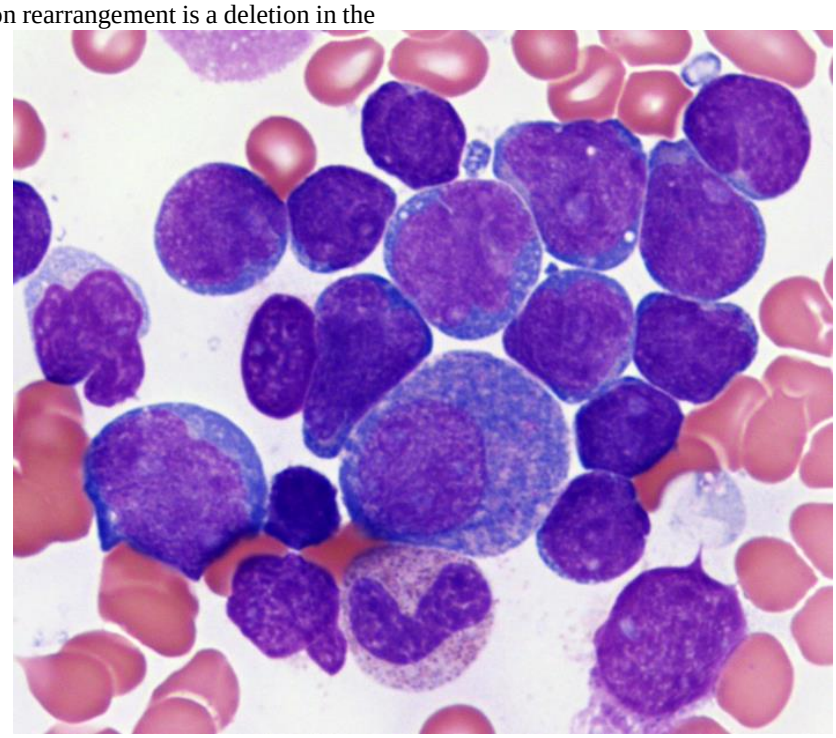

Figure 1: Bone marrow aspirate smears reveal increased blasts which are small to medium in size with high nuclear-to-cytoplasmic ratios, round to irregular nuclei, smooth chromatin, and scant basophilic agranular cytoplasm. Some background maturing myeloid cells are also present in this case.

Overall, these common B-ALL gene rearrangements, which occur at a rate of approximately 60% in non-Down syndrome patients, only occur at a rate of approximately 20% in ALL-DS. Instead, ALL-DS is more likely to have a normal karyotype (with the exception of the constitutional trisomy 21). In those without normal karyotypes, DS-ALL are more likely to be low hyperdiploid, with common acquired changes including +X and/or del(9p) (Forestier et al., 2008; Lundin et al., 2014).

Genes

JAK2 activating mutations have been found in approximately 20% of ALL-DS, with the most common mutations occurring at or around amino acid R683 in the pseudokinase domain (Bercovich et al., 2008; Kearney et al., 2009; Gaikwad et al., 2009); however, other JAK2 mutations have been identified in ALL-DS, as have mutation in other JAK genes including JAK1 (Mullighan et al., 2009). These JAK2 mutations are found predominantly in those with CRLF2 gene rearrangements. JAK2 mutation status has not been found to correlate with outcome. The JAK2 mutations are thought to act in concert with the CRFL2 gene rearrangements, resulting in cytokine-independent growth and leukemogenesis (Mullighan et al., 2009).

In addition to mutations in the JAK-STAT pathway, mutations in the RAS/receptor tyrosine kinase (RTK) pathway genes such as KRAS and NRAS have been identified at a rate of approximately 35%; these mutations are mutually exclusive of the JAK2 mutations (Nikolaev et al., 2014). However, similar to the JAK2 mutations, the RAS pathway mutations often occur in the setting of CRLF2 rearrangements. Nikolaev et al. (2014) also identified mutations in cohesion complex genes, epigenetic modifiers/remodellers of DNA or chromatin, classical tumor suppressor genes, and lymphoid

differentiation factors/markers.

Activating mutations in CRLF2 can also occur, again usually in the setting of CRLF2 gene rearrangements (Hertzberg et al., 2010).

Deletions in IKZF1 are also often found in DS-ALL, estimated at 24-35% (Hertzberg et al., 2010; Buitenkamp et al., 2012), as are deletions in the PAX5 gene (12-22%) (Kearney et al., 2009; Lundin et al., 2012; Buitenkamp et al., 2012). Patients with an IKZF1 deletion or a PAX5 deletion have decreased overall survival compared to those without these deletions (Buitenkamp et al., 2012).

Treatment

ALL-DS is treated similarly to ALL in those without Down syndrome. However, some additional modifications and supportive care guidelines are often employed in their treatment, including the use of discontinuous dexamethasone during delayed intensification and adding leucovorin rescue after intrathecal methotrexate (Maloney, 2011). Down syndrome patients have increased susceptibility to methotrexate, with higher rates of mucositis, gastrointestinal toxicity, and hepatotoxicity. Some trials have decreased the methotrexate dosage, increasing the dose only if tolerated. Additionally, Down syndrome patient have a higher risk of hyperglycemia after corticosteroids and asparaginase therapy due to alterations in glucose metabolism.

Prognosis

In some studies, children with ALL-DS have been found to have poorer outcomes than children with ALL without Down syndrome, sometimes demonstrating increased induction failures, higher relapse rates, and increased therapy-related mortality. The poorer outcomes are thought to be due, at least in part, to increased sensitivity to methotrexate side effects, and increased susceptibility to infection. The latter susceptibilities are thought to be enhanced by the inherent immunodeficiencies of Down syndrome. However, more recently, with appropriate prognostic group identification based upon favorable and unfavorable cytogenetic features, ALL-DS has been found to have comparable outcomes to ALL not associated with Down syndrome (Maloney et al., 2010; Maloney, 2011). In addition, Buitenkamp et al., 2014 found favorable prognostic factors to include diagnosis < 6 years of age and a WBC 9/L.

In those who relapse, ALL-DS has a lower event-free survival and lower overall survival compared to those with ALL without Down syndrome, usually due to induction deaths and treatment-related mortality (Meyr et al., 2013). These relapses usually occur late (more than 6 months after completion of therapy) (Meyr et al., 2013; Buitenkamp et al., 2014).

In those who undergo a hematopoietic cell transplant (HCT), post-transplant relapse often occurs, with a probability of 54% within 3 years in one cohort, with an overall survival at 3 years of 29% (Hitzler et al., 2014).

Genes involved and proteins

JAK2 (janus kinase 2)

Location
9p24.1

Protein
Protein tyrosine kinase involved in cytokine receptor signaling pathways.

Somatic mutations
Mutations often occur in the pseudokinase domain at or around R683 in exon 16 and result in constitutive kinase activity.

IKZF1 (Ikaros family zinc finger 1)

Location
7p12.2

Protein
Zinc-finger DNA-binding protein that is a transcription factor associated with chromatin remodeling. It is a transcription regulator of lymphocyte differentiation.

Somatic mutations
Usually deletions.

PAX5 (paired box gene 5)

Location
9p13.2

Protein
Paired box transcription factor which has a role in B-cell differentiation, involving regulation of CD19.

Somatic mutations
Usually deletions.

KRAS (Kirsten rat sarcoma 2 viral oncogene homolog)

Location
12p12.1

Protein
RAS oncogene that is a member of the small GTPase family.

NRAS (neuroblastoma RAS viral oncogene homolog)

Location
1p13.2

Protein
RAS oncogene that is a member of the small GTPase family.

CRLF2 (cytokine receptor-like factor 2)

Location
Xp22.33

Protein
Encodes cytokine receptor-like factor 2 which is a lymphoid signaling receptor that dimerizes with interleukin-7 receptor (IL7R) to form a receptor for thymic stromal lymphopoietin (TSLP). This complex (CRLF2/IL7R/TSLP) can stimulate cell proliferation through activation of STAT3 and STAT5.

Somatic mutations
Most commonly, translocations occur with P2RY8 or IGH. In addition to the translocations, in some patients activating mutations in CRLF2 can also occur.

P2RY8 (purinergic receptor P2Y, G-protein coupled, 8)

Location
Xp22.33

Protein
Encodes a G-protein coupled purinergic receptor (P2Y, G-protein coupled, 8).

Somatic mutations
Through an interstitial deletion, the first noncoding exon of this gene hybridizes with the coding region of CRLF2.

IGH (Immunoglobulin Heavy)

Location
14q32.33

Protein
Immunoglobulin heavy chain.

Somatic mutations
Through a translocation, this gene hybridizes to CRLF2.

Result of the chromosomal anomaly

Hybrid gene

Note
The P2RY8/CRLF2 fusion is much more common than the IGH/CRLF2 fusion.

Description
An interstitial deletion in the pseudoautosomal region 1 (PAR1) of Xp22.3/Yp11 occurs in the P2RY8/CRLF2 fusion, hybridizing the first noncoding exon of P2RY8 to the entire coding region of CRLF2 [del(X)(p22.33p22.33)/del(Y)(p11.32p11.32)].
Alternatively, a translocation occurs between CRLF2 and IGH resulting in t(X;14)(p22;q32)/t(Y;14)(p11;q32).

Detection
These fusions can be detected by FISH or RT-PCR.

Fusion protein

Oncogenesis
Results in overexpression/dysregulated expression of CRLF2.

References

Bercovich D, Ganmore I, Scott LM, Wainreb G, Birger Y, Elimelech A, Shochat C, Cazzaniga G, Biondi A, Basso G, Cario G, Schrappe M, Stanulla M, Strehl S, Haas OA, Mann G, Binder V, Borkhardt A, Kempski H, Trka J, Bielorei B, Avigad S, Stark B, Smith O, Dastugue N, Bourquin JP, Tal NB, Green AR, Izraeli S. Mutations of JAK2 in acute lymphoblastic leukaemias associated with Down's syndrome. Lancet. 2008 Oct 25;372(9648):1484-92

Bruwier A, Chantrain CF. Hematological disorders and leukemia in children with Down syndrome. Eur J Pediatr. 2012 Sep;171(9):1301-7

Buitenkamp TD, Pieters R, Gallimore NE, van der Veer A, Meijerink JP, Beverloo HB, Zimmermann M, de Haas V, Richards SM, Vora AJ, Mitchell CD, Russell LJ, Schwab C, Harrison CJ, Moorman AV, van den Heuvel-Eibrink MM, den Boer ML, Zwaan CM. Outcome in children with Down's syndrome and acute lymphoblastic leukemia: role of IKZF1 deletions and CRLF2 aberrations. Leukemia. 2012 Oct;26(10):2204-11

Forestier E, Izraeli S, Beverloo B, Haas O, Pession A, Michalová K, Stark B, Harrison CJ, Teigler-Schlegel A, Johansson B. Cytogenetic features of acute lymphoblastic and myeloid leukemias in pediatric patients with Down syndrome: an iBFM-SG study. Blood. 2008 Feb 1;111(3):1575-83

Gaikwad A, Rye CL, Devidas M, Heerema NA, Carroll AJ, Izraeli S, Plon SE, Basso G, Pession A, Rabin KR. Prevalence and clinical correlates of JAK2 mutations in Down syndrome acute lymphoblastic leukaemia. Br J Haematol. 2009 Mar;144(6):930-2

Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet. 2000 Jan 15;355(9199):165-9

Hertzberg L, Vendramini E, Ganmore I, Cazzaniga G, Schmitz M, Chalker J, Shiloh R, Iacobucci I, Shochat C, Zeligson S, Cario G, Stanulla M, Strehl S, Russell LJ, Harrison CJ, Bornhauser B, Yoda A, Rechavi G, Bercovich D, Borkhardt A, Kempski H, te Kronnie G, Bourquin JP, Domany E, Izraeli S. Down syndrome acute lymphoblastic leukemia, a highly heterogeneous disease in which aberrant expression of CRLF2 is associated with mutated JAK2: a report from the International BFM Study Group. Blood. 2010 Feb 4;115(5):1006-17

Hitzler JK, He W, Doyle J, Cairo M, Camitta BM, Chan KW, Diaz Perez MA, Fraser C, Gross TG, Horan JT, Kennedy-Nasser AA, Kitko C, Kurtzberg J, Lehmann L, O'Brien T, Pulsipher MA, Smith FO, Zhang MJ, Eapen M, Carpenter PA. Outcome of transplantation for acute lymphoblastic leukemia in children with Down syndrome. Pediatr Blood Cancer. 2014 Jun;61(6):1126-8

Kearney L, Gonzalez De Castro D, Yeung J, Procter J, Horsley SW, Eguchi-Ishimae M, Bateman CM, Anderson K, Chaplin T, Young BD, Harrison CJ, Kempski H, So CW, Ford AM, Greaves M. Specific JAK2 mutation (JAK2R683) and multiple gene deletions in Down syndrome acute lymphoblastic leukemia. Blood. 2009 Jan 15;113(3):646-8

Lange B. The management of neoplastic disorders of haematopoiesis in children with Down's syndrome. Br J Haematol. 2000 Sep;110(3):512-24

Lundin C, Forestier E, Klarskov Andersen M, Autio K, Barbany G, Cavelier L, Golovleva I, Heim S, Heinonen K, Hovland R, Johannsson JH, Kjeldsen E, Nordgren A, Palmqvist L, Johansson B. Clinical and genetic features of pediatric acute lymphoblastic leukemia in Down syndrome in the Nordic countries. J Hematol Oncol. 2014 Apr 11;7:32

Lundin C, Hjorth L, Behrendtz M, Nordgren A, Palmqvist L, Andersen MK, Biloglav A, Forestier E, Paulsson K, Johansson B. High frequency of BTG1 deletions in acute lymphoblastic leukemia in children with down syndrome. Genes Chromosomes Cancer. 2012 Feb;51(2):196-206

Maloney KW. Acute lymphoblastic leukaemia in children with Down syndrome: an updated review. Br J Haematol. 2011 Nov;155(4):420-5

Maloney KW, Carroll WL, Carroll AJ, Devidas M, Borowitz MJ, Martin PL, Pullen J, Whitlock JA, Willman CL, Winick NJ, Camitta BM, Hunger SP. Down syndrome childhood acute lymphoblastic leukemia has a unique spectrum of sentinel cytogenetic lesions that influences treatment outcome: a report from the Children's Oncology Group. Blood. 2010 Aug 19;116(7):1045-50

Meyr F, Escherich G, Mann G, Klingebiel T, Kulozik A, Rossig C, Schrappe M, Henze G, von Stackelberg A, Hitzler J. Outcomes of treatment for relapsed acute lymphoblastic leukaemia in children with Down syndrome. Br J Haematol. 2013 Jul;162(1):98-106

Mullighan CG, Collins-Underwood JR, Phillips LA, Loudin MG, Liu W, Zhang J, Ma J, Coustan-Smith E, Harvey RC, Willman CL, Mikhail FM, Meyer J, Carroll AJ, Williams RT, Cheng J, Heerema NA, Basso G, Pession A, Pui CH, Raimondi SC, Hunger SP, Downing JR, Carroll WL, Rabin KR. Rearrangement of CRLF2 in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia. Nat Genet. 2009 Nov;41(11):1243-6

Nikolaev SI, Garieri M, Santoni F, Falconnet E, Ribaux P, Guipponi M, Murray A, Groet J, Giarin E, Basso G, Nizetic D, Antonarakis SE. Frequent cases of RAS-mutated Down syndrome acute lymphoblastic leukaemia lack JAK2 mutations. Nat Commun. 2014 Aug 8;5:4654

This article should be referenced as such:

Chisholm KM. Acute lymphoblastic leukemia in Down syndrome. Atlas Genet Cytogenet Oncol Haematol. 2018; 22(8):341-345.