GENETIC ALTERATIONS IN ACUTE LYMPHOBLASTIC LEUKEMIA

UAB

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Introduction

Acute Lymphoblastic Leukemia (ALL) is a neoplasm of immature lymphoid progenitors, characterized by **clonal expansion** of leukemic cells in the **bone marrow** (BM). It can affect **both children and adults**, but is more prevalent between ages of 2 and 5 years. The majority of ALL cases are **aneuploidy** or harbor recurring **structural chromosomal rearrangements** that are important in initiating events in leukemogenesis and which subdivides between the subtypes B and T, but that are insufficient to explain the biology and heterogeneity of ALL. For that reason it is **necessary** a thorough **study** about **genetics** of the disease.

Methods and objectives

Bibliographic search of reviews and original articles in databases such as PubMed (NCBI) has been made in order to accomplish the following goals: present the current situation of the disease and how the genetic study has allowed us to understand the disease as well as the risk stratification, and develop new therapies.

Clinical diagnostic

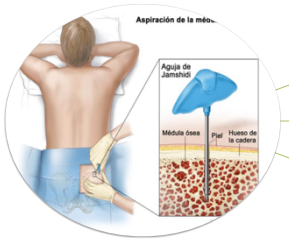


Figure 1: Bone marrow aspiration and biopsy from National Cancer Institute <http://www.cancer.gov> [26/05/2015]

- **Morphology**
  - **ALL-L1**
  - **ALL-L2**
  - **ALL-L3**
- **Immunophenotype**
  - **ALL-B:** CD19, CD20, CD22, CD24, CD79a, CD10, cIgM and mIgM
  - **ALL-T**: CD2, CD3, CD5, CD1a, CD4 and CD7
- **Genetic analysis**
  - **Conventional cytogenetics**
  - **Molecular cytogenetics**
  - **PCR and CGH**

Techniques

1956 The human chromosome number is 46

1985 Invention of polymerase chain reaction (PCR)

Development of conventional cytogenetics

1982 Fluorescence *in situ* hybridation was developed

1992 Comparative genomic hybridation (CGH) was developed

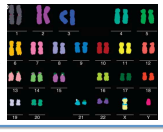


Figure 2: Human male Karyotype after hybridization with of a seven-fluorochrome M-FISH mix from Naturel protocols <www.nature.com> [26/05/2015]

GENETIC ALTERATIONS

Cytogenetic alterations	Genetic lesion	Associated clinical features and specifics treatments	Prognosis
Changes in chromosomal Number 25%	Hyperdiploidy (>50)	20% with *FLT3* activation	Good prognosis
	Hypodiploidy (<44)	High frequency of *RAS* pathway and IKAROS gene family mutations	Poor prognosis
Structural abnormalities chromosome 50%	**B-ALL**		
	BCR-ABL t(9;22)	Associated with *IKZF1* or *CDKN24* deletions. Treatment with tyrosine kinase inhibitors like imatinib but resistance develops rapidly. *BCR-ABL1-like* with deletions in *IKZF*, rearrangements in *CRLF2* and *JAK* mutations.	Poor prognosis
	MLL rearrangements	Unregulated *FLT3*. Use of cytarabine for some rearrangements. Treatment with *FLT3* inhibitors like sorafenib or crenalanib.	Improved outcome
	ETV6-RUNX1 t(12;21)	Intensive chemotherapy that includes asparaginase. Sometimes present iAMP21with multiple copies of *RUNX1*. Current development of treatment in the UK	Good prognosis
	E2A-PBX1 t(1;19)	Increased incidence in African Americans. Intensified chemotherapy	Generally excellent prognosis
	T-ALL		
	NOTCH1 t(7;9)	Resistant tumours, gain of function that activates *MYC*	
	HOX rearrangements	Elevated expression; HOX11 inhibition of PP2A and PP1 phosphatases	HOX11 T-ALL has better prognosis than other T-ALL molecular
	TAL1/SCL t(1;14)	Dimerize *E2A* and HEB transcription factors, blocking T cell differentiation	Good and poor outcomes
	LYL1 t(7;19)	Dimerize E2A and HEB transcription factors, blocking T cell differentiation	

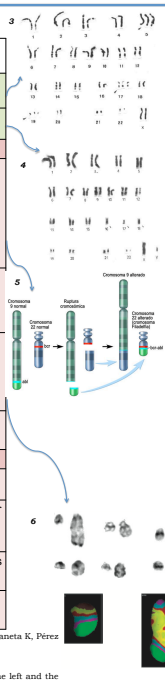


Figure 3 and 4: Hyperdiploidy (3) and Hypodiploidy karyotype from Quintero M, Rojas-Atencii A, Ruiz A, González M, Herrera J, Atencio F, Delgado W, Urdaneta K, Pérez F, 2003. Anomalías cromosómicas en pacientes venezolanos con mieloma múltiple. *Scielo*. Vol. 44

Figure 5: Chromosomal translocation *BCR-ABL* from Leucemia linfoblástica aguda infantil: Tratamiento (PDQR). Instituto Nacional del Cáncer. p. 1-71

Figure 6: *iAMP21*. A) Partial G-banded karyotypes showing pairs of chromosomes 21 from six patients. In each pair the normal chromosome 21 is on the left and the abnormal homologue is on the right. B) G-banding and mBAND partial karyotypes of normal left and abnormal right chromosomes 21 from iAMP21 from Harrison C.J, 2009. Cytogenetics of paediatric and adolescent acute lymphoblastic leukaemia. *British Journal of haematology*. Vol. 144, pg. 147-156

Cytogenetic technologies permit the detection of different types of chromosomal and genetic abnormalities. There are three types of chromosomal aberrations: those involving changes in chromosome number, those with structural abnormalities and those that present a normal karyotype. The genetics of these chromosomal alterations allow us to know the incidence and prevalence of each one, use it for monitoring the disease, learn about the biology of the disease, the risk stratification and the potential markers for therapy. **Hyperdiploidy**, with gain of at least 5 chromosomes, is one of the most frequent alterations in childhood, and is associated with a favourable outcome. Hyperdiploidy includes **quasitri/tetraploidy**. However, **hypodiploidy** with fewer than 44 chromosomes is associated with poor prognosis. The recurring **chromosomal rearrangements** differentiate, B-ALL or T-ALL and the new rearrangements are critical for leukemogenesis and commonly perturb genes encoding regulators of haematopoiesis, tumour suppressors, oncogenes or tyrosine kinases, but in most cases they are primary events that need others to produce disease. Moreover, some patients present a **normal karyotype (diploid)**, which has an improved outcome.

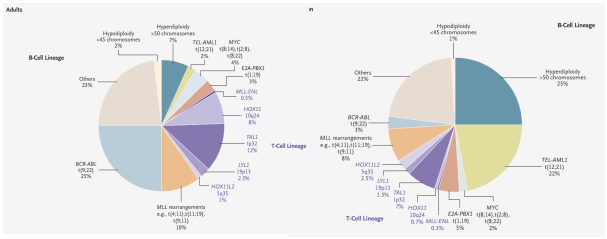
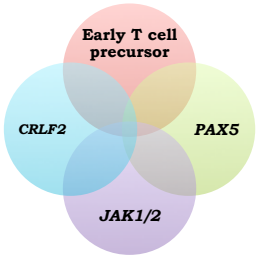


Figure 7. Estimated Frequency of Specific Genotypes of ALL in Children and Adults from Pui C.H, Relling M.V, Pharm D, Downing J.R, 2004. Mechanisms of disease Acute Lymphoblastic Leukemia. *The New England Journal of Medicine*. Vol. 350, p. 1535-1548

Novel alteration



Novel perspectives

- **Personalized medicine**
- **There is no consensus on what constitutes an optimal treatment**
- **Develop less toxic treatments while preserving earlier gains in efficacy**
- **Studies have begun to identify a number of polymorphisms, such as *ARID5B, IKZF1, CEBPE* and *CDKN2A***
- **New epigenetic studies**

Conclusion

ALL is the most common and heterogeneous neoplasm in childhood and its also affects adults. Early diagnosis is important to perform a good treatment and get complete remission.

Genetics have allowed us to identify a large number of chromosomal alterations that are associated with biological features. The genetics alterations has been used to define B-ALL and T-ALL, prognostic and risk stratification.

Conventional cytogenetic analysis should be a mandatory routine examination.

Further genetic study must be carried out to understand the disease and create specialized treatments.

References

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