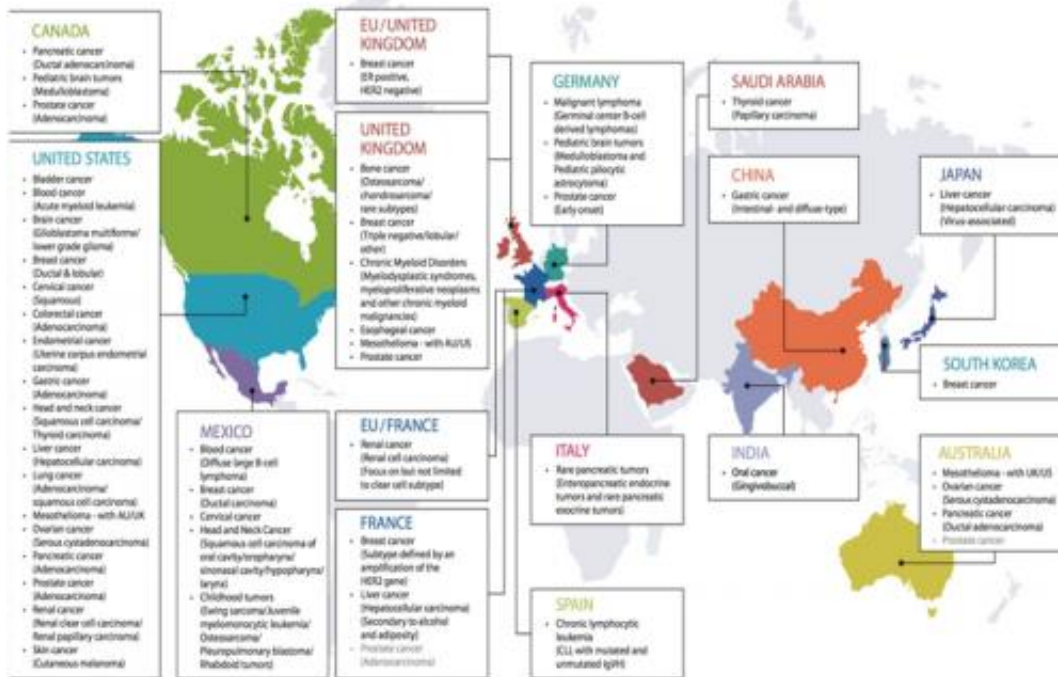


Researchers unravel the first epigenomes of chronic lymphocytic leukemia

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Researchers of the University of Oviedo have contributed to decipher the first epigenomes of chronic lymphocytic leukemia. Professor of Biochemistry and Molecular Biology Carlos López-Otín and two members of his team: Xose S. Puente and Víctor Quesada, researchers of the University Institute of Oncology of the Principality of Asturias (IUOPA), have taken part, together with researchers Elías Campo and

Iñaki Martín-Subero, in a study published today in *Nature Genetics*, which presents a new perspective in cancer research.

This study integrates the whole epigenome and genome sequencing of leukemia patients. Researchers have identified the cells that give rise to the disease, and have discovered new molecular mechanisms involved in its development, thereby improving diagnosis.

This research is part of the project of the Spanish CLL Genome [Consortium](#), which has had the collaboration of researchers from the European BLUEPRINT Consortium for the study of epigenomes. In the last two years, the Spanish Consortium—included in the International Cancer Genome Consortium—has published two outstanding works in *Nature* and *Nature Genetics* that have characterized a mutational genome map associated with this disease.

The State Secretary for Research, Development and Innovation of the Ministry of Economy and Competitiveness, Carmen Vela, presented today, together with the coordinators of the study, –Carlos López-Otín, from the University of Oviedo, and Elías Campo, from the Hospital Clínic and the University of Barcelona–, and director of the study –Iñaki Martín-Subero, from the University of Barcelona and the Institute for Biomedical Research 'August Pi i Sunyer', the latest results of the Leukemia Genome project. The director of the Institute for Health Carlos III, Joaquín Arenas, also took part in the presentation.

The State Secretary for R&D&I has highlighted the "importance of this study" and has stated that projects like this "show the quality of our science and our scientists". Any advance in this area is important, but if it is led by Spanish scientists, it's even more gratifying. Spain develops quality research and we are working to make sure this continues in the future".

Elías Campo has stated that the previous studies of the Consortium were focused on the analysis of mutated genes involved in the development of the disease. "In this new study —he added— we have a new perspective of the epigenome, which has allowed us to identify the cells of origin of this kind of leukemia and new mechanisms involved in its development".

"Our previous genetic studies identified over 1.000 mutated genes in the chronic lymphocytic leukemia, whereas this epigenomic analysis has revealed over a million epigenetic changes in this disease. This unexpected finding indicates that the epigenome of cells suffers a massive shift in the process of cancer development", says Dr. López-Otín.

One of the great innovations of this study is that the genome and epigenome have been analyzed in parallel. Epigenetics is defined as the science that studies the set of [molecular mechanisms](#) that activate or inactivate genes. As explained by López-Otín, "the genome is a repository of information whereas the epigenome is responsible for executing this information for the proper functioning of cells".

Thanks to the new sequencing technologies available in the National Center for Genomics Analysis of Barcelona and the use of high-density micro arrays, this new study has decoded for the first time the complete epigenome of the disease and has led to unexpected discoveries. "Until now, most epigenetic studies were focused on the analysis of a limited fraction of the genome, which were considered crucial for gene expression. Our results clearly show that most of the epigenetic alterations take place in regions of the genome that had never been studied before", explains the director of the study, Iñaki Martín-Subero.

This study appears a few weeks after the publication of the results of the ENCODE project, which shows that most regions of the genome that were considered as 'junk DNA' really contain a large number of

regulatory regions of the gene activity. "Once integrated our new data with the ENCODE Project, we are surprised to observe that most epigenetic alterations in leukemia occur in these new regulatory regions of the genetic activity", highlighted Martín-Subero.

This work of the Spanish Leukemia Genome Consortium is a clear example of interdisciplinary [biomedical research](#) which involved experts in epigenetics, genetics, molecular biology, bioinformatics, clinical pathology and hematology. "This integrative approach and working together is a key to the success of our Consortium", commented Elías Campo.

The objective of the Consortium is to provide a detailed description of the molecular alterations associated with the disease which may result into benefits for patients. The study presented today offers a new approach to improve the diagnosis of the disease. According to Dr. Martín-Subero, "we have found out that epigenetic patterns can classify patients with chronic Lymphocytic leukemia in three groups with a different clinical course". "A very interesting aspect is that each group has a leukemia clinical epigenetic memory of the cell from which it was originated. Types of Leukemia with worse prognosis seem to be derived from immature lymphocytes, while the least aggressive ones are associated with mature lymphocytes", he detailed.

Main features of the study:

- Thanks to the next-generation sequencing technologies available at the National Center for Genomic Analysis this study has characterized the epigenome of leukemia in a relatively short time.
- The vast amount of data generated in this project has required new methodology that has been mainly developed by the research

group of Dr. Martín-Subero and the Bioinformatics group of the National Center for Genomic Analysis of Barcelona.

- The Hospital Clínic of Barcelona has been working on the Chronic Lymphocytic Leukemia for decades, which has allowed the Consortium to have biological samples and clinical data of hundreds of patients that have been used to define the clinical relevance of the epigenomic study of this disease.
- In addition to studying the [epigenome](#) of 139 patients suffering from [chronic lymphocytic leukemia](#), researchers have also analyzed several subtypes of normal blood lymphocytes, which has allowed for the identification of the cellular origin of [leukemia](#) groups with a different clinical course.
- The work of the experts in several scientific disciplines has meant new information to improve the diagnoses of patients.

Provided by University of Oviedo

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