GENETIC PREDISPOSITION TO LEUKEMIA IN DOWN SYNDROME CHILDREN

Scientific dissemination project

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Objectives

The main objective of this project was to create an informative video about the relationship between Down Syndrome and leukemia, to explain the parents and relatives of the affected children the genetic basis of both conditions. Since it has been oriented to a non-specialized public, it has been done in an understandable fashion for people without knowledge in genetics. The information is supported with animation drawings that complement the explanation given.

Popularization interest

Although the presence of people with Down syndrome is very common, in our society many do not know the origin of this condition or certain pathologies that are associated, as is the case of leukemia. Despite having been designed for a specific public, this video is divided in four parts that can serve as a source of information for any person interested. Hence, it can be used to understand basic concepts of genetics, as well as to know genetic factors predisposing to and causing Down syndrome and leukemia.


Bibliographic research


Software selection


Talk to affected families


Write the script

Prepare the pictures

Video production


Record the audio


Video edition

VIDEO CONTENT

Genetics Basic Concepts

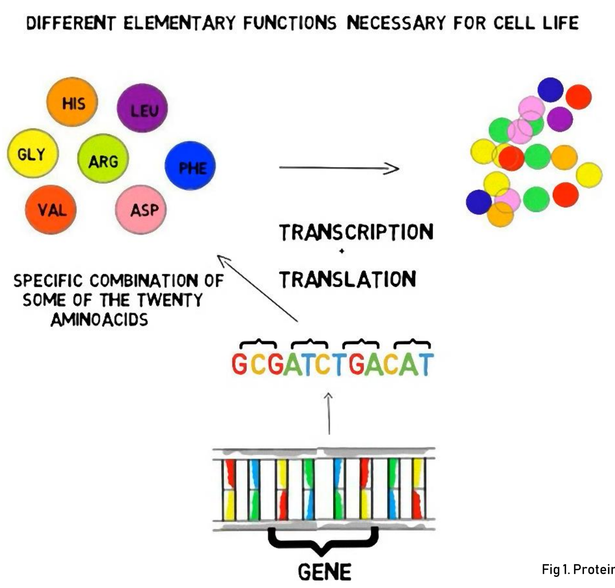

Fig 1. Protein biosynthesis

Certain basic concepts of genetics considered necessary to fully understand the video in its entirety have been explained. Some of those are the components of DNA, its organization, the formation of proteins (Fig.1) and the process of differentiation.

Down Syndrome

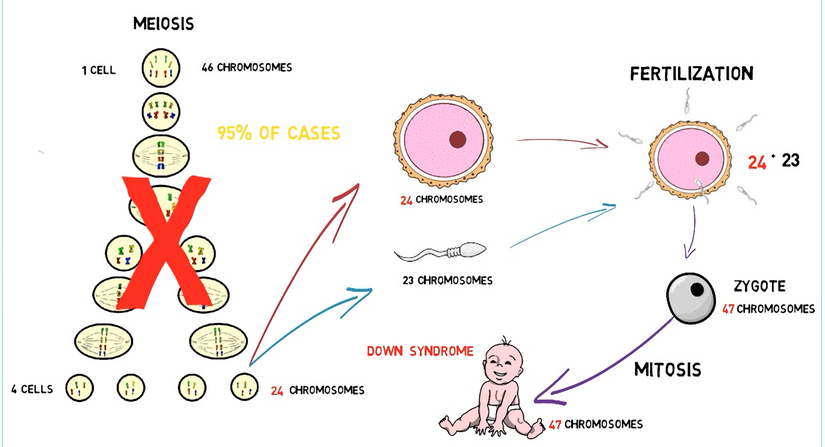

Fig 2. Meiotic nondisjunction of chromosome 21 (normally in the female gamete) originates DS on 95% of cases

A brief clinical introduction to Down Syndrome and the associated pathologies has been carried out. Subsequently, the three main processes that originate trisomy 21 have been detailed: meiotic nondisjunction (Fig. 2), translocation and mosaicism.

Leukemia

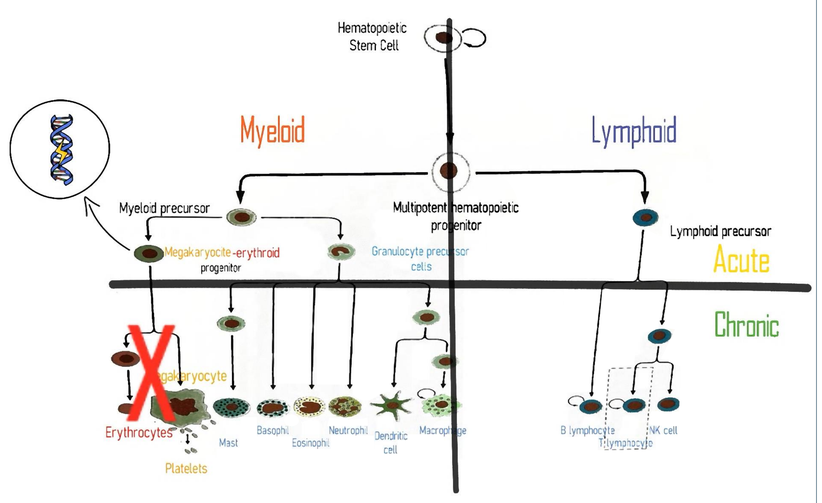

Fig 3. The hematopoietic process and the four main leukemia types

What is cancer and the three types of genes whose alteration causes a carcinogenic process have been described: oncogenes, tumor suppressor genes and DNA repair genes. The concepts explained after that are the hematopoietic process, leukemia and its four main types (Fig. 3).

Genetic predisposition to leukemia in Down Syndrome

Transient myeloproliferative disorder (TMD)

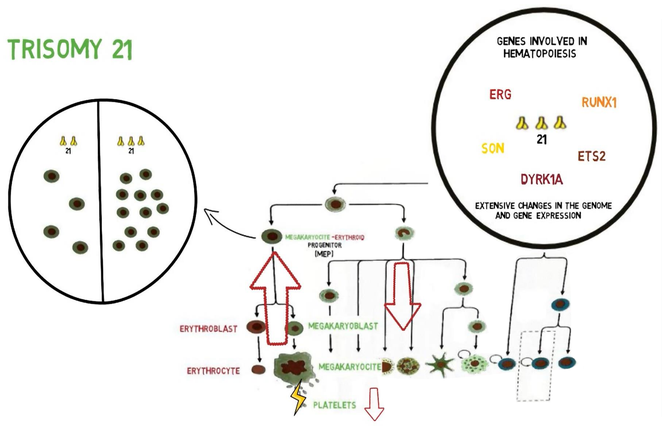

Fig 4. Effect of trisomy 21 in hematopoiesis

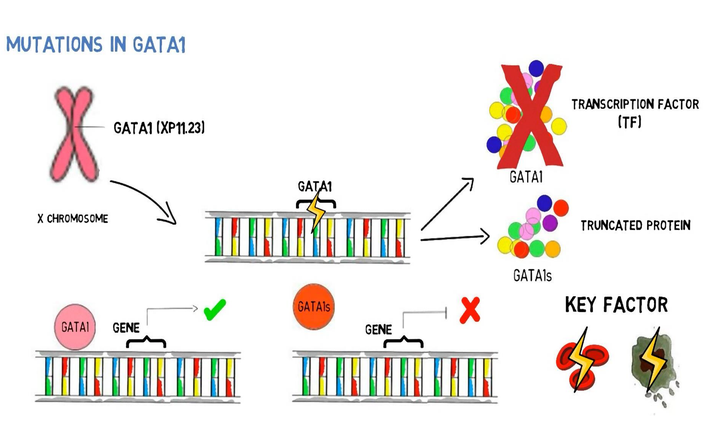

Fig 5. Effect of the apparence of mutations in the GATA1 gene

TRISOMY 21 + GATA1 MUTATED = TMD

DS children have a 500-fold increased risk to develop Acute myeloid leukemia (AML). Nearly 10% of DS newborns develop TMD in their 3 to 7 first days of life. TMD is a clonal pre-leukemia characterized for an accumulation of immature megakaryoblasts in fetal liver, bone marrow and peripheral blood, and a decrease in the number of platelets and erythrocytes. TMD is a cooperative process between trisomy 21 and mutations acquired in *GATA1* gene.

Although it is not entirely clear, it is believed that the overexpression of some genes involved in haematopoiesis present in chromosome 21 and the alterations caused by this extra chromosome originate an over-proliferation of hematopoietic stem cells (HSC) and myeloid progenitors. This provokes an increase in the number of megakaryocyte-erythroid progenitors (Fig. 4).

In addition, fetal liver hematopoietic microenvironment favours the appearance and maintenance of mutations in *GATA1*. This gene codifies for a zinc-finger DNA-binding transcription factor with a key role in erythrocyte and megakaryoblast differentiation (Fig. 5).

Mutations that originate TMD and AMKL are indels and point mutations in exons 2 and 3. They are N-terminal truncating mutations, which prevents the synthesis of *GATA1* and allows for the expression of the isoform *GATA1s*. It lacks the transactivation domain, so it is less effective regulating differentiation of erythrocytes and megakaryoblasts.

Therefore, trisomy 21 and the presence of truncating mutations in *GATA1* are enough and necessary for the development of TMD, which normally reverts spontaneously within 3 months of life.

Acute megakaryoblastic leukemia (AMKL)

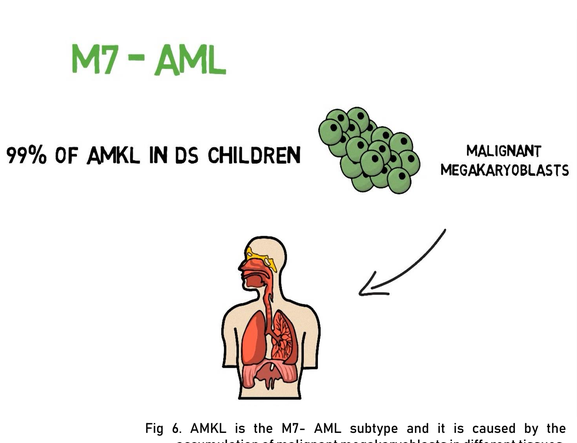

Fig 6. AMKL is the M7- AML subtype and it is caused by the accumulation of malignant megakaryoblasts in different tissues

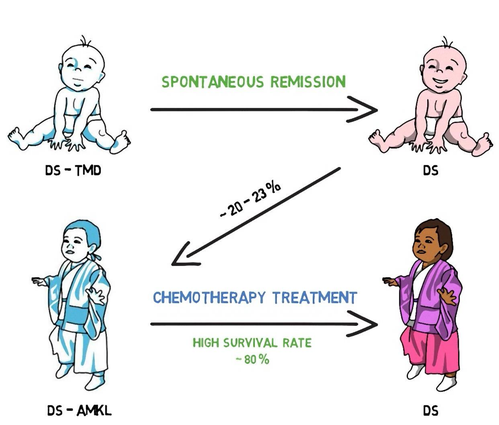

Fig 7. Transition from TMD to AMKL

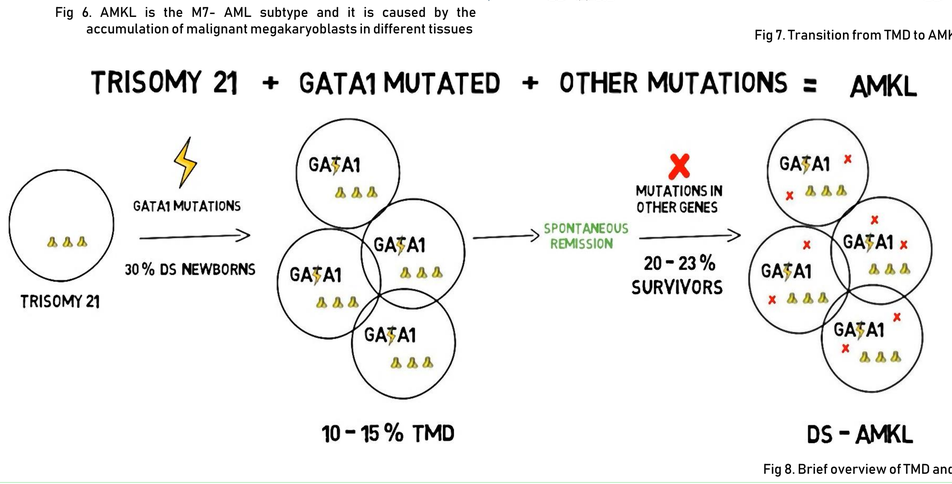

Fig 8. Brief overview of TMD and AMKL

20% of survivors end up developing AMKL within 5 years. It is ocasionated by the inadequate elimination of all the blasts with trisomy 21 and mutated *GATA1*, and in them new mutations appear. Some studies using whole-exome sequencing and whole-genome sequence showed that AMKL evolves thanks to additional mutations in other genes. These include cohesin components, *CTCF*, epigenetic regulators such as *EZH2* and *KANSL1*, and common signaling pathways such as the *JAK* family kinases and multiple *RAS* pathway genes (Fig. 8).

Children with AMKL need chemotherapy treatment, but they usually respond quite well and present a high survival rate (Fig. 7).

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Watch Video

https://www.youtube.com/watch?v=8u6LB9veuWM