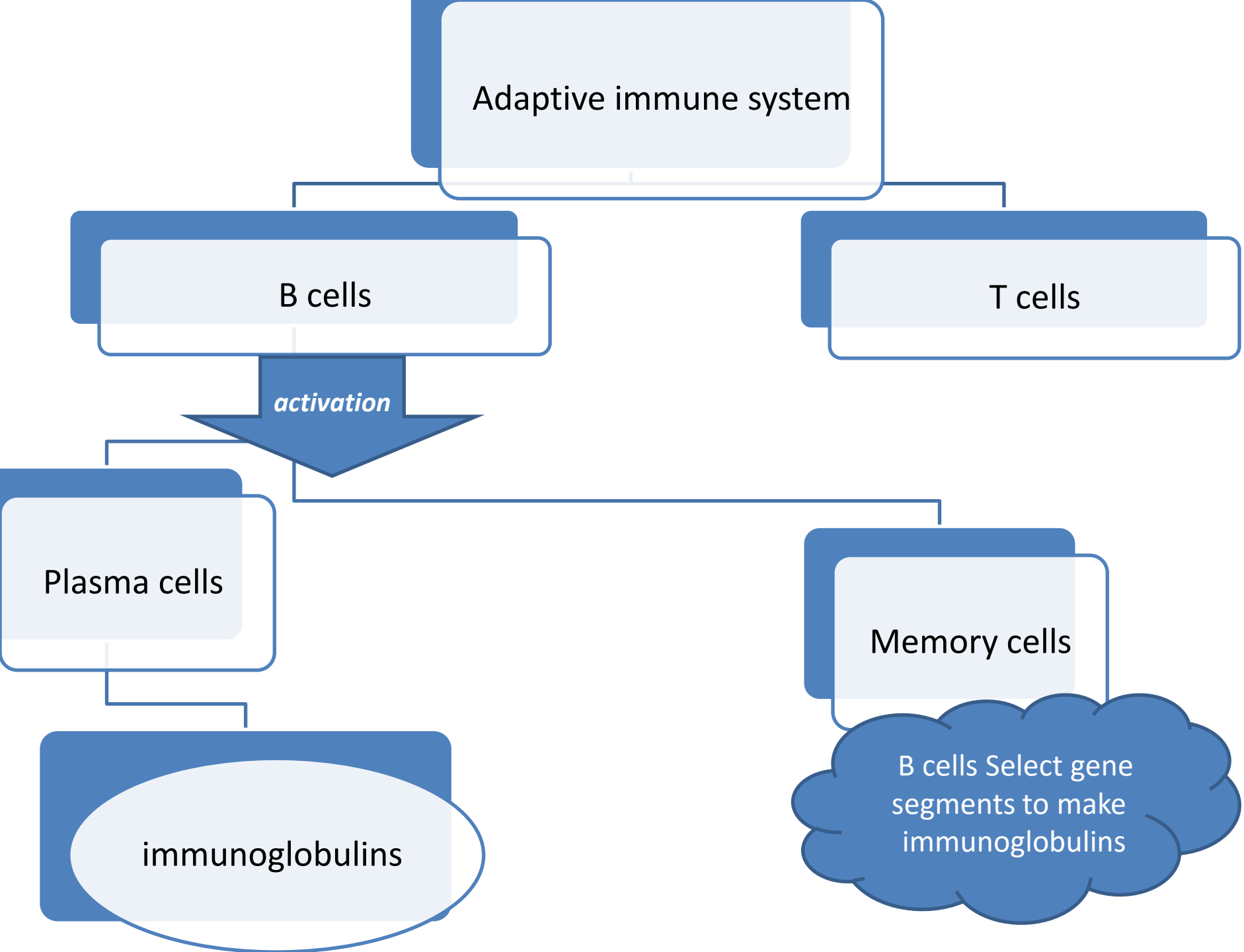
Omenn Syndrome

A form of SCID


Adaptive immune system
B cells
T cells
activation
Plasma cells
Memory cells
immunoglobulins
B cells Select gene segments to make immunoglobulins

Activation process

Where does it occur ?

B cells are *activated* in the bone marrow

T cells are *activated* in the thymus

how ?

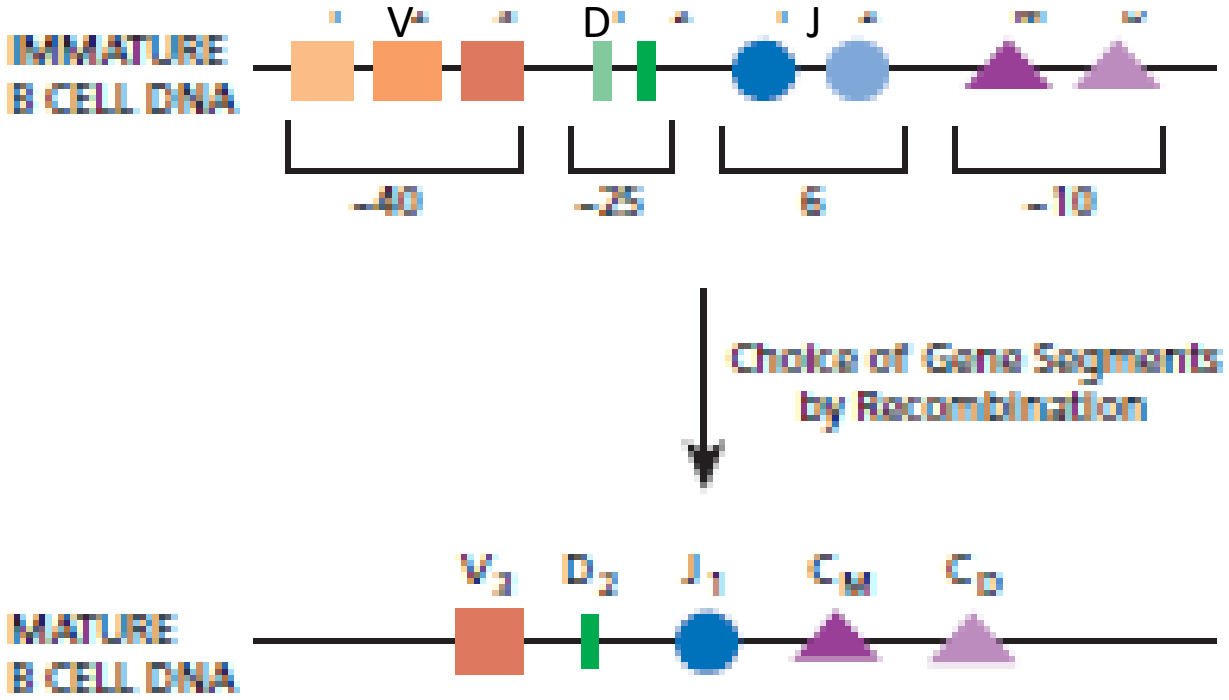
By the assembly of gene segments to make the variable sequence which encode for(V) region of ***heavy and light chains of the antibodies* OR *alpha and beta chains of T-CELL receptor***

This process is called VDJ recombination

VDJ recombination

Immunoglobulin genes are found on chromosome 14.
T-cell receptor genes are found on chromosome 7

V: variability region – includes 40 different types (or genes)
D: diversity region – includes 25 different types
J: joining region – includes 6 types
C: constant region (determines the class of the antibody)



Recombination Events

To make the variable region For **the light chains of immunoglobulins and the alpha chains of TCR:**

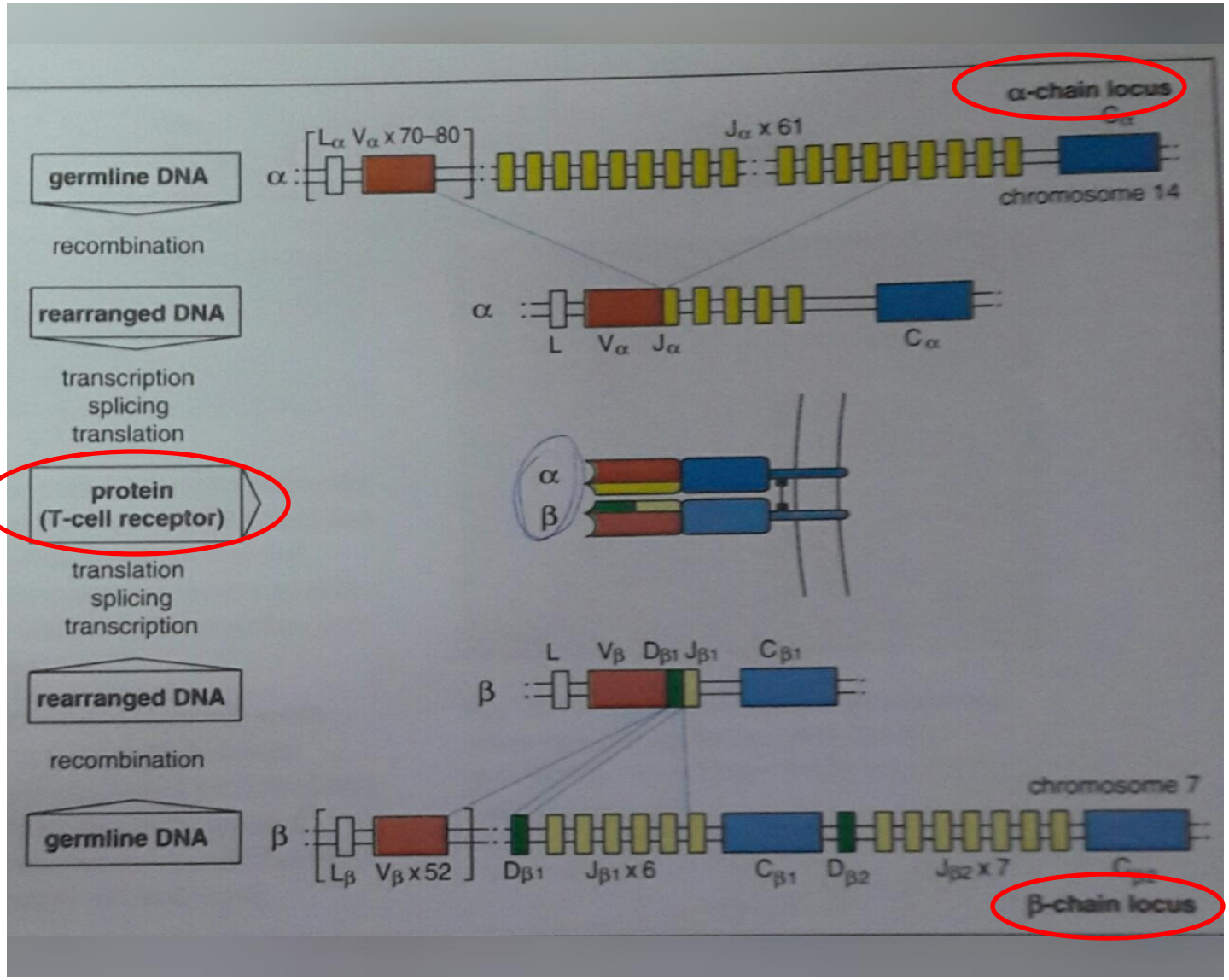
(V) and (J) gene segment are joined

To make the variable region For **the heavy chains of immunoglobulins and the beta chains of TCR :**

1- D and J gene segment are joined first

2-followed by joining of a V gene segment to form VDJ

The DNA between the rearranging gene segments is **deleted** from the chromosome.


α-chain locus
germline DNA
recombination
rearranged DNA
transcription
splicing
translation
protein
(T-cell receptor)
translation
splicing
transcription
rearranged DNA
recombination
germline DNA
chromosome 14
chromosome 7
β-chain locus

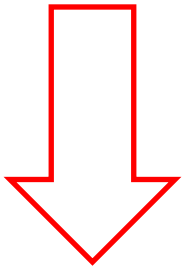
The **vast diversity** in the antibodies and the TCR is generated because:

There are ***many different V D J segments*** in the germline genome so we have million possible combination

small insertions or deletions of nucleotides at the joins between V D J segments also play a role in diversity !

V(D)J RECOMBINATION is initiated by **RAG1** RAG2 enzymes ……

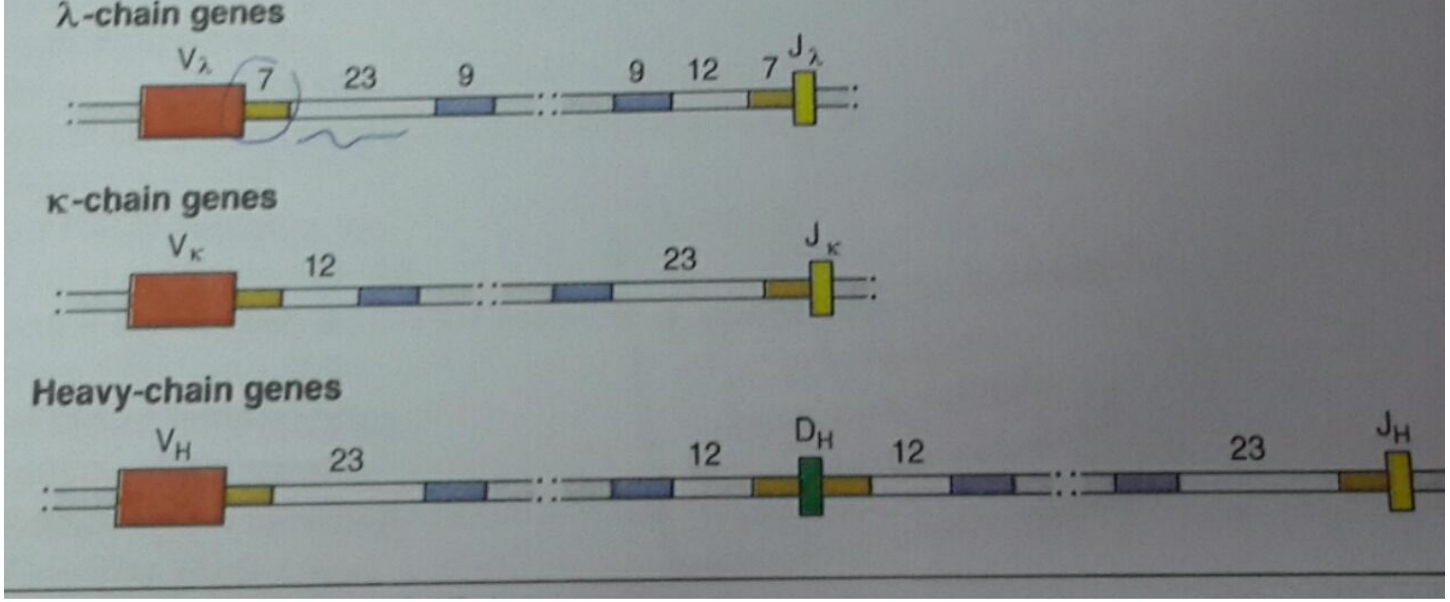
*they **recognize canonical DNA sequence** (**recombination signal sequence**)



Consist of a **heptamer (CACAGTG)**

Followed by a **spacer 12 or 23 base**

Then a **nonamer (ACAAAAGTG)**



1- RAG1 binds to the **nonamer** then RAG2 bind to the **heptamer**

2- the DNA sequence between the heptamer and the coding segment is then **nicked**

3- a **break in the dsDNA** occurs

4- DNA repair protiens carry out the **rejoining process** of the VDJ gene segments.

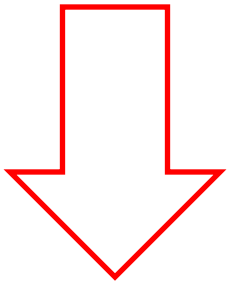
What happens **if either of the RAG genes is knocked out** by homologous recombination in mice?

The mice will have severe combined immunodeficiency.(B and T cells development is completely abolished)

Mutations in RAG1 RAG2 have been found in cases of human sever combined immunodeficiency.

RAG enzymes first discovered in mice and later identified in humans

Certain **Missense mutations in the RAG genes** result in *partial enzymatic activity*



will give rise to an immunodeficiency disease called **Omenn Syndrome**

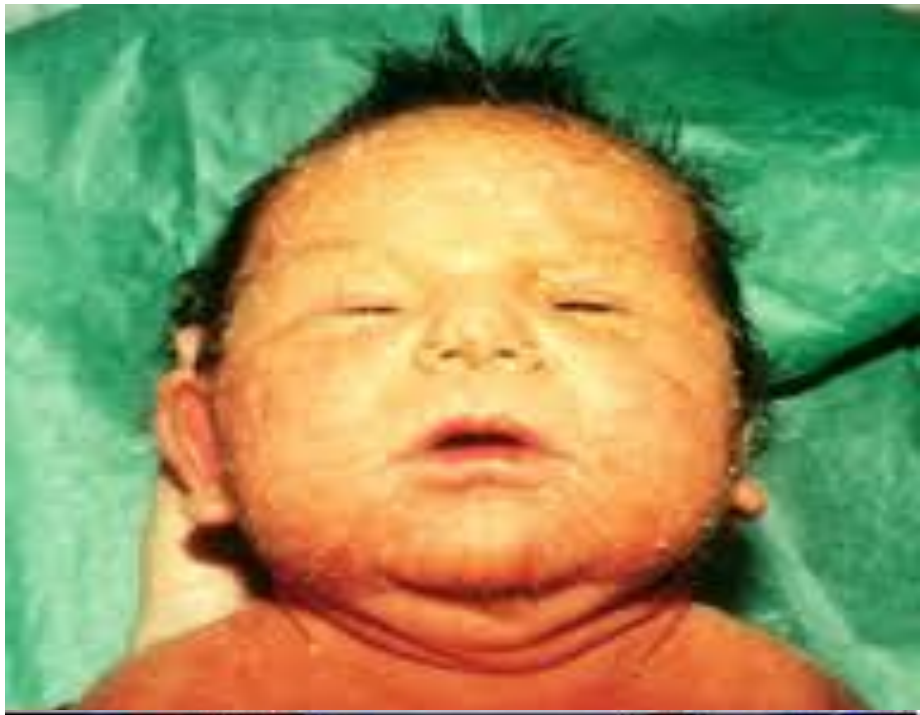
A form of sever combined immunodificeincy (SCID)

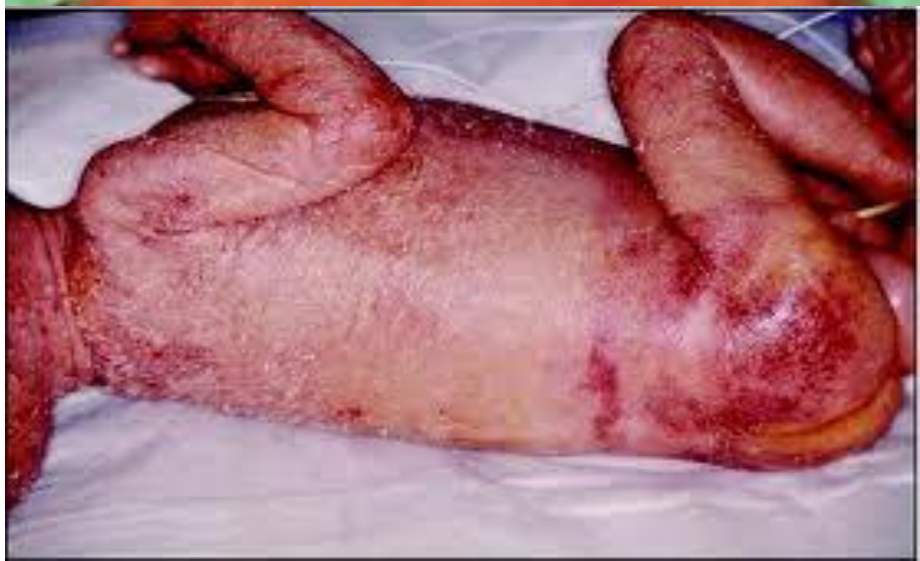
The case of **Ricardo Reis**

At birth : appeared normal healthy baby (weight length and head circumference were normal)

On the 27th day after birth : he developed a red raised popular rash on his legs

Over the next 7 days the rash spread all over his body





Ricardo was admitted to the hospital and **the diffuse rash was worst on his face** but **also covered his trunk and extremities** (**erythroderma**: *bright red rash*)

He had **purulent conjunctivitis** (yellow discharge from his eyes)

Small red blisters were present on his palms and soles of his feet

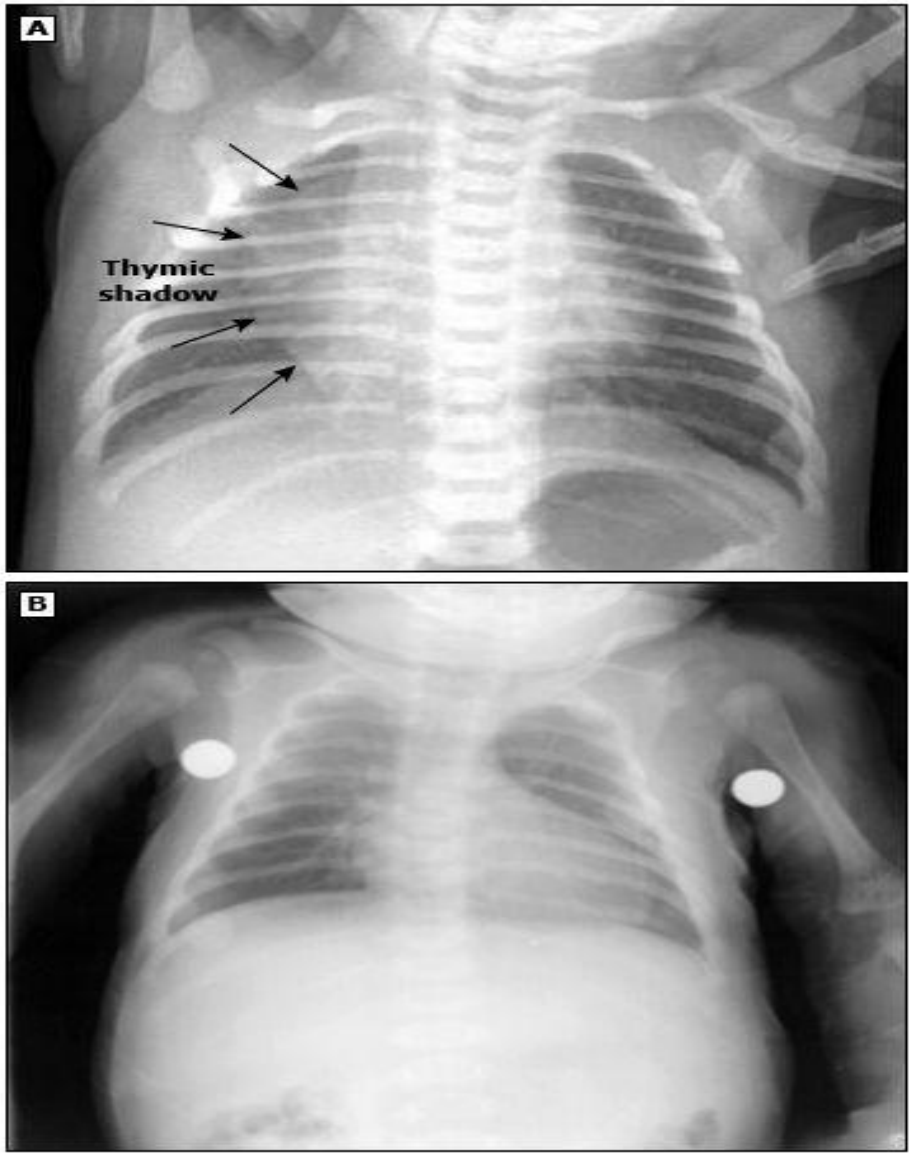
Ricardo Blood tests

Hemoglobin concentration	15.4g/dl	normal
Platlet count	46000	Slightly elevated
WBC count	8000/microL	Normal
Eosinophils %	**56%**	**Abnormal (eosinophilia)**
Neutrophil %	**15%**	**Abnormal**
Lymphocyte %	**6%**	**Abnormal**
IgE level	**7500IU /microL (<50 normally)**	**Highly elevated IgE level**
IgG level	**55mg/dl (400mg normally)**	**Low IgG level**

Bone marrow examination : preponderance of eosinophil precursors

Skin biopsy: the skin was inflitrated with large number of eosinophils, lymphocytes, and macrophages. Blood vessels was surrounded by large number of cells

X-ray of the chest : clear lung and normal cardiac shadow **no thymic shadow.**



The top chest radiograph shows a normal thymic shadow. The bottom radiograph shows absence of the thymic shadow in an infant with severe combined immunodeficiency (SCID)

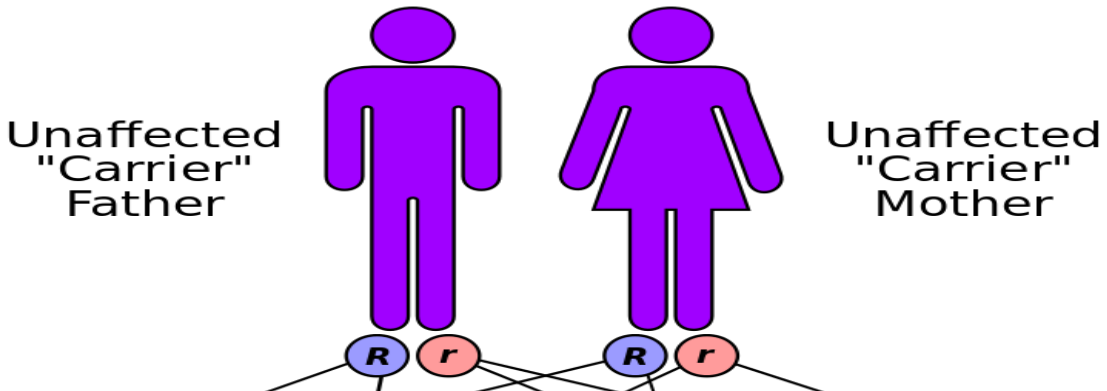
Family history…..

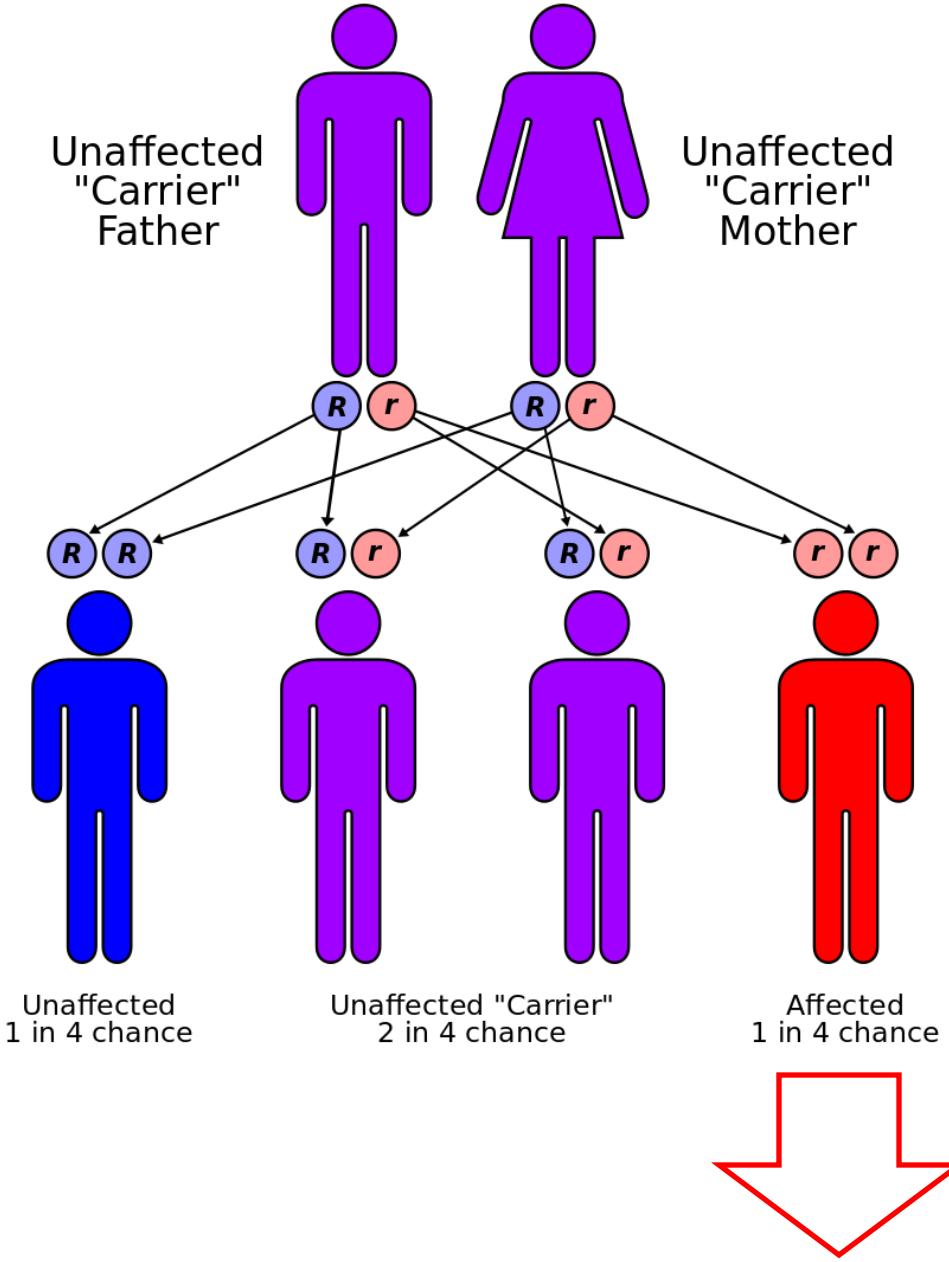
The parents were first cousins from Portuguese origin

Both parents are normal

The parents had **3 normal children** BUT had **2 children a(boy and a girl)who died at the 1st month soon after the onset of a similar rash!!**

This indicates autosomal recessive inheritance of the defect





The defect is not dominant: both parents are normal *(to be dominant one parent have to be affected)*

Family history helped in determine the mode of inheritance : **autosomal recessive inheritance**

Not X-linked recessive: The defect affected both (male, female)

Treatment recommended by ***hematology consultant*** : **vinblastin**

Despite this therapy, Ricardo's condition rapidly **worsened**

1- enlarged lymph nodes in the neck and groin

2- pus accumulated in the skin behind the ear

3-opportunistic infections was noted (staphylococcus aureus and candida albicans).

Then an **immunologist** was consulted and he ordered blood tests that revealed : **absence of B cells and a paucity of T cells**

lymphocytes responded poorly to stimulation with anti-cd3 monoclonal antibody. No cells were found that reacted with anti-cd19 which detect b cells.

All lymphocytes were CD3+ (90% expressed MHC class II) A marker of T-cell activation

↓

Activated T-cells expanded within the lymph node(explain enlargement of the lymph nodes)

Ricardo's T-cells were found to be **oligoclonal(**small number of different T-cell receptors)

(this was determined with **Jβ probe**-southern blotting-)

Vitro Analysis of VDJ recombination revealed that Ricardo had only **20% of the normal RAG**

enzyme function

Suggesting a defect in RAG1 or RAG2

RAG1 and RAG2 genes were sequenced

Missense mutation was found in the RAG1 gene

Unfortunately……

- While these studies were being carried out, Ricardo developed Pneumocystis carinii pneumonia and **died of respiratory failure**

To sum up ….

Omenn syndrome is an autosomal recessive severe combined immunodeficiency associated with missense mutations in RAG genes (so that only partial enzyme activity was expressed)

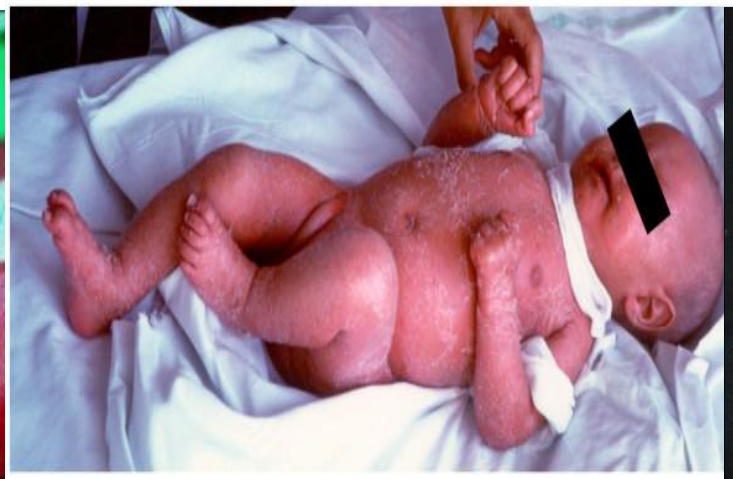
The RAG genes are essential for gene recombination in the **T-cell receptor** and **B-cell receptor**, and loss of this ability means that the immune system has difficulty recognizing specific pathogens

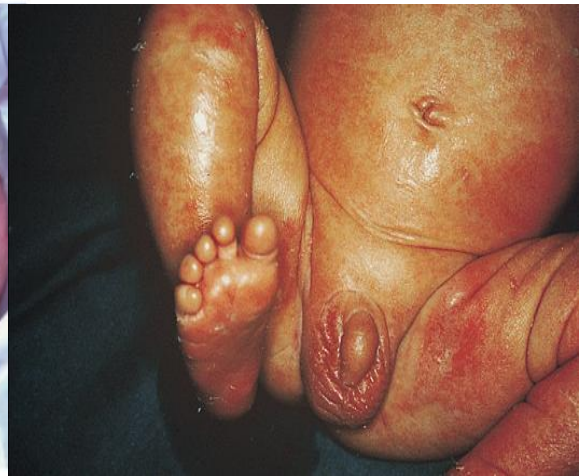
The syndrome is characterized by....

early onset erythroderma chronic inflammation of the skin, which **appears as a red rash**

Other symptoms include : failure to thrive, **enlarged lymph nodes, spleen, ,and liver**, diarrhea

Eosinophilia , low immunoglobulin levels (except **IgE, which is elevated**), low T cell levels (oligoclonal), and no mature B cells





What cause the bright red rash (**erythrodermia**)??

The T-cells that are present are activated (express MHC class II and homing receptors for the skin)

In the skin activated T-cells **secrete chemokines that attract other inflammatory cells like eosinophil and macrophages into the skin**

The privascular inflammation in the skin causes the **blood vessels to dilate**…..increase blood flow… appear as a **bright red rash(erythrodermia)**

How do you explain elevated IgE and eosinophilia ??

The few T-cells that were able to rearrange their TCR gene must have had **a phenotype that secrete large amount of IL4 and IL5**

Required for switching to IgE synthesis.
The few B-cells (undetectable)have been induced to switch the immunoglobulin class to IgE

Is required for recruitment of eosinophils

Treatment??

The only treatment for Omenn syndrome is **bone marrow transplantation**. **Without treatment, it is rapidly fatal in infancy**.

Some patients have been rescued with transplant of HLA-identical bone marrow.

Thank you !