Omenn Syndrome

Topics: definition, VDJ recombination, RAG1+2 , Ricardo case.  
\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
- What is Omenn syndrome?  
It is an autosomal recessive disorder that happens due to a missense mutation affecting newborns’ immune systems leading to their death before completing their first month.  
\_\_\_\_\_\_\_

-Recombinase activating genes (RAG-1 and RAG-2)  
These genes encode RAG1 and RAG2 enzymes which are important for B and T cells to complete their process of maturation. How ? They initiate a process called V(D)J recombination. This process will produce :  
1- Antibodies, in B cells. 2- Tcell receptor, in T cells.

On the chromosome , there are many gene segments ( V gene segment, D gene segment, J gene segment). Each segment has many variant genes.

V(D)J recombination process is simply a process that collects one gene from each segment and fuses them together to produce one complete gene that will ENCODE the VARIABLE REGION of heavy ,light chains in antibodies and alpha, beta subunits in T cell receptors. (The DNA between the rearranging gene segments will be deleted). When the variable region is ready, it will join the constant region producing one fused gene that will be transcripted then translated into antibodies or Tcell receptor.

Rag1+2 enzymes will bind on specific sequences that cover those gene segments to **rearrange them** in order to produce a fused gene that will encode the chains needed to get Antibodies and Tcell receptors. (There are several million possible combinations).

There are two specific sequences:

1. heptamer (CACAGTG)

followed by a spacer of 12 or 23 bases and then

2-nonamer (ACAAAAGTG)   
>> RAG1 enzyme binds the nonamer and RAG2 enzyme binds the heptamer INITIATING the recombination process.

\_\_\_\_\_\_

Review:  
antibodies have heavy and light chains , T cell receptors (TCR) have alpha and beta chains. If those chains are not synthesized> >> No antibodies nor TCR >> immunodeficiency >> death.

Our bodies synthesize B and T cells to protect us from infections. During development of these cells , if the newborn has a mutated RAG1+2 genes , his immunity is weak, he will become susceptible to infections and thus he will die.  
\_\_\_\_\_\_\_\_\_\_\_  
-VDJ Racombination.  
I recommended watching this short video at first..

<https://www.youtube.com/watch?v=QTOBSFJWogE>   
-Regarding synthesis of antibodies : the heavy chain will be synthesized alone (As we know, the VARIABLE REGION (produced by the V(D)J recombination process) will be joined with the constant region to get one chain) and so as the light chain( the variable region will join the constant region) then 2 heavy chains and 2 light chains will be joined together and form ONE antibody.

The variable region of heavy chain is synthesized by VDJ recombination ( the three segments are involved) .

The variable region of light chain is synthesized by VJ recombination ( no D segment ), meaning that the fused gene produced by the recombination process does not have a D gene from D segment.  
That’s why they put the D in brackets naming the process V(D)J.  
  
-Regarding synthesis of Tcell receptors :

The TCR consists of two chains: alpha and beta subunits.

The variable region of beta chain is synthesized by VDJ recombination (like the heavy chain).  
The variable region of alpha chain is synthesized by VJ recombination (like the light chain).



RAG-1 and RAG-2 are Involved in both Ig and TCR recombination

Alpha TCR subunit is made Of V and J segements only (Same as Ig light chain) .Beta subunit made of V, D, and J segments. (Same as Ig heavy chain)

-There are other proteins involved in this process (Ku70,

Ku80, DNA-PKcs, Artemis, DNA ligase IV (LIG4), XRCC4, and Cernunnos/XLF) , they are recruited by RAG1+2 enzymes.

Ricardo case :

We said that this syndrome is autosomal recessive, we need both alleles to be mutated. Ricardo’s parents are carriers so there is a susceptibility of 25% of their children to have the disease.  
Main manifestations are :

1-bright red rash, purulent conjunctivitis

2-Eisonophilia(56%), low lymphocyte count, No B cells and very low T cells.

3-Low Immunofolbulins except for IgE. (important\*\*)  
>>As only a partial ability of V(D)J recombination is retained by the mutated enzyme.

4-Enlarged lymph nodes.

\_\_\_\_\_\_\_\_\_\_\_\_  
Treatment : Bone marrow transplantation.

Ismail Kokash.