X linked Severe Combined Immunodeficiency

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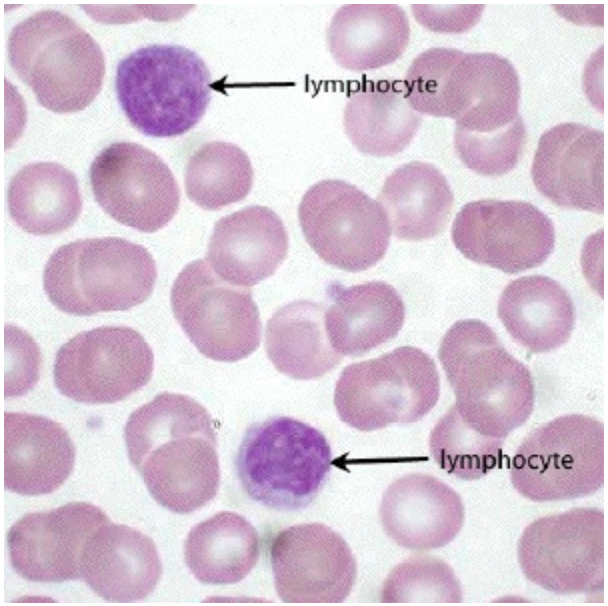
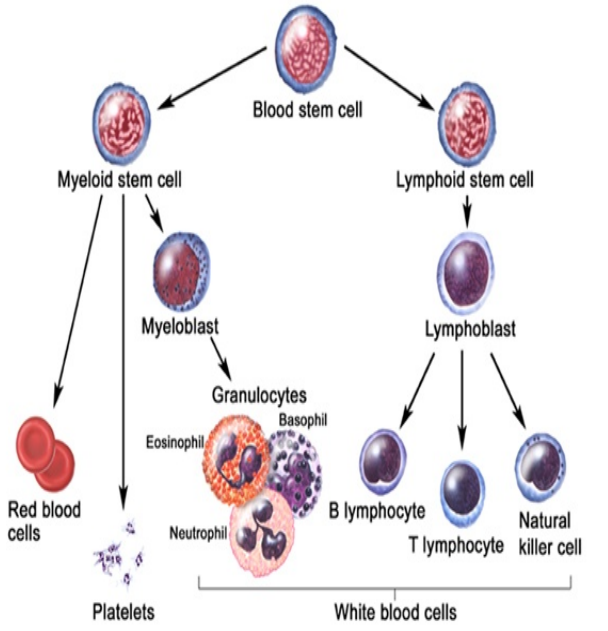
Genomics and Medicine

What Is X Linked SCID ?

- X linked recessive
- Combined cellular and humoral immunodeficiency disorder
- Lack of T and Natural Killer (NK) Lymphocytes
- Non functional B lymphocytes
- Affects 1 in 50,000 to 100,000 newborns
- Also called "bubble boy disease"

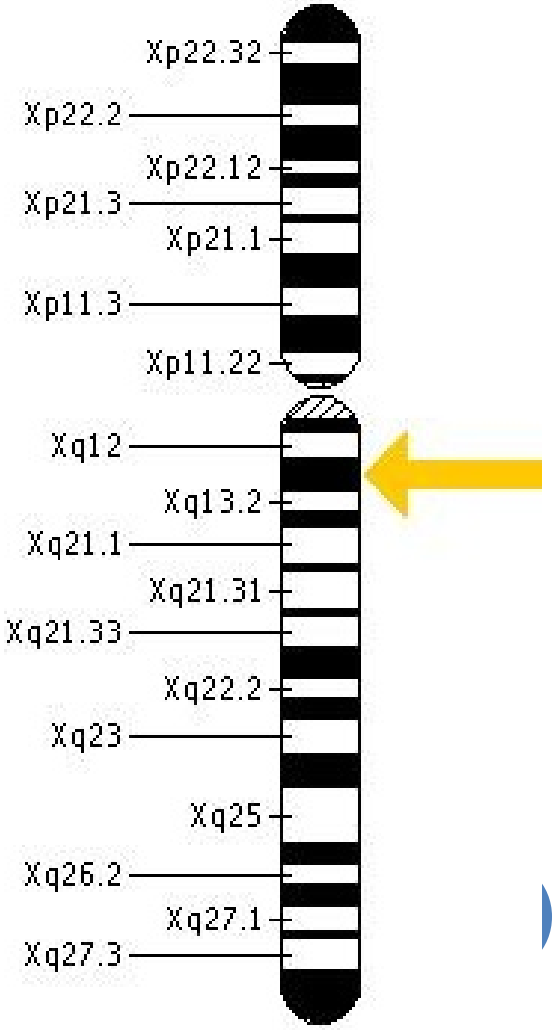




THE BOY IN THE BUBBLE

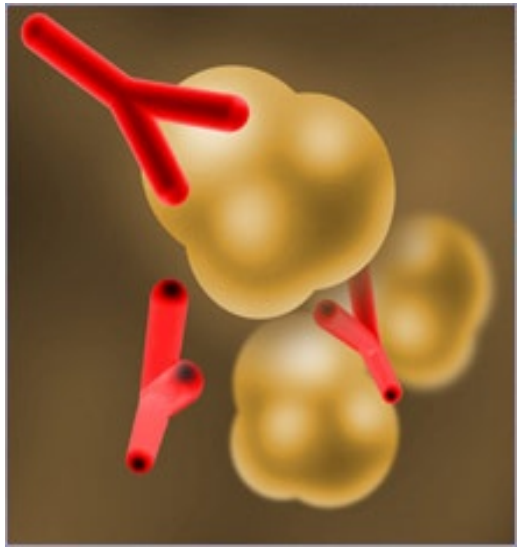
THE DEFECTIVE GENE

- Mutation in the Interleukin-2 Receptor Gamma gene
- Chromosomal Location: Xq13
- Mutation affects the growth, maturation and differentiation of lymphocytes.



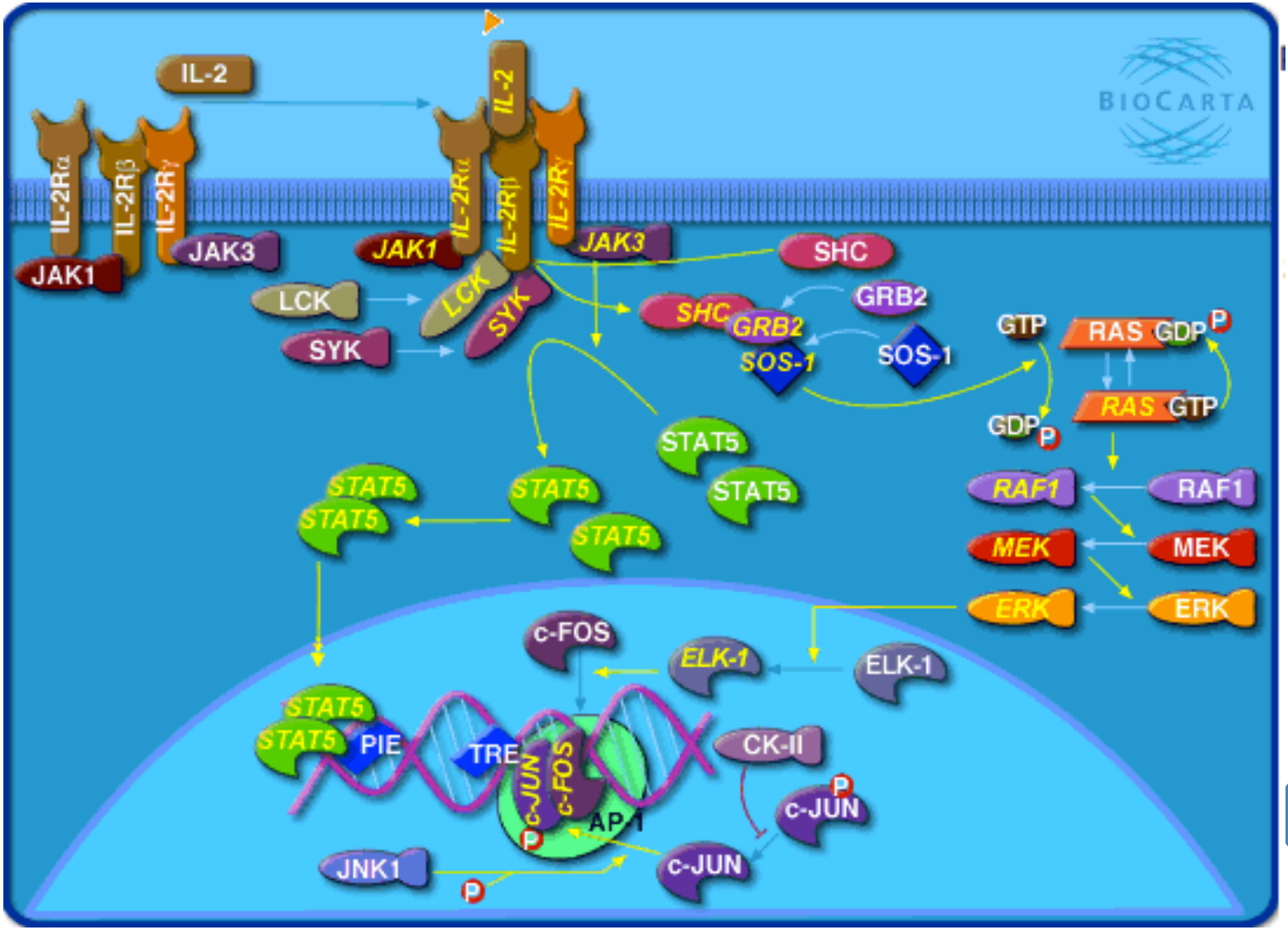
What Is The Il-2R Protein?

- Interleukin-2
  - Cytokine
  - Powerful mitogen
  - Involved in autocrinal signalling



- Interleukin Receptors:
  - Trans-membrane protein in the cell surface membrane of lymphocytes.
  - Binds to IL-2

IL-2 Signaling Pathway



IL2 SIGNALLING PATHWAY

- JAK/STAT Pathway
- JAK (Janus Kinase): phosphorylates tyrosine residues
- STAT (Signal Transducer and Activator of Transcription): Dimerises and binds to the DNA in the cell to activate transription.
- SH2 domains (**S**rc **H**omology 2 domain): Recognises protein with phosphotyrosine residues

SYMPTOMS

- Infections very early in life, before three months of age.
  - Thymic hypoplasia
  - Oral candidiasis
  - Pneumonitis
  - Moniliasis, a telltale sign of X-SCID
  - Chronic Diarrhoea
  - Skin rashes

- Persistence of infections despite conventional treatment

Classical Diagnosis

- **Lymphocyte counts**

Cell Type	X SCID affected	Normal
T cells	200	5500
B Cells	1300	800
NK Cells	<100	800

- **Lymphocyte functional tests**
  - No antibody responses to vaccines and infectious agents
  - No T-cell responses to mitogens.
- **Immunoglobulin concentration tests**
  - Low levels of IgA and IgM.
  - Declining levels of IgG

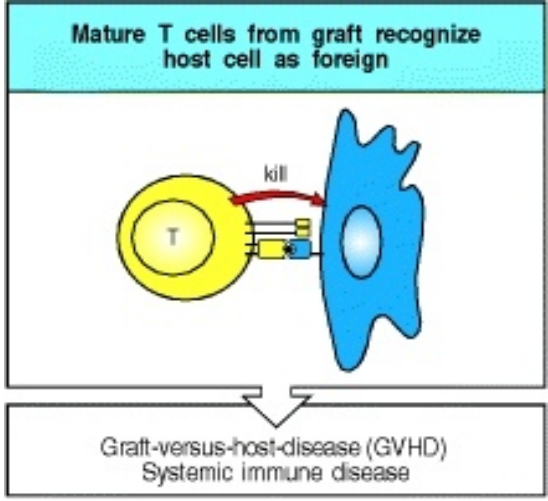
Novel diagnosis

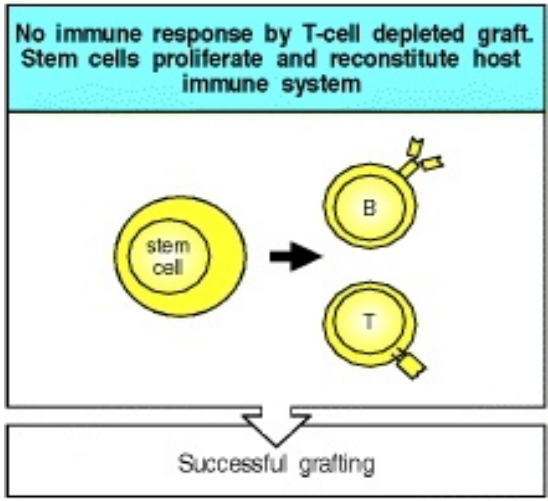
- **Molecular Genetic Testing**
  - Sequence analysis of the *IL2RG* coding region
- **Targeted mutation analysis:**
  - Detection of large deletions and complex mutations
  - For individuals in whom mutations are not detected by sequence analysis.
- **Carrier Testing**
  - For at risk females
  - X chromosome inactivation studies
- **Prenatal Testing**
  - Possible for pregnancies of women who are carriers of X SCID

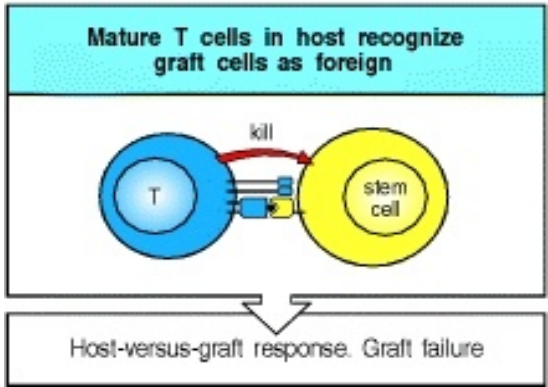
Classical Treatment

- **Bone Marrow Transplantation:**
  - HLA-matched bone marrow
  - Successful 90% of the infants with X-SCID
  - Possible Complications: Graft-versus-host disease (GVHD)

- **Immunoglobulin Administration :**
  - For those who fail to develop functional B lymphocytes.







Novel Treatments

- **Gene Therapy**
  - Transduction of the missing gene to hematopoietic stem cells using viral vectors
  - Overall efficacy similar to or even better than BMT
  - No risks of GVHD
  - Potential Risk: Leukemia

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